Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	158	oxypurinol or alloxanthine	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/01 14:42
S1	4	"4539323"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:14
S2	6	kivlighn.IN.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:17
S3	60665	Johnson.IN.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:17
S4	41	Johnson-richard.IN.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:19
S5	50	Mazzali.IN.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:19
S6	1	Mazzali-Marilda.IN.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:19
S7	3866	allopurinol or carprofen	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:20
S8	48629	hypertension	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:20
S9	596	S7 and S8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:21
S10	470	"xanthine oxidase inhibitor"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:21
S11	48629	S8 and S8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:21

S12	53334	S10 adn S8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:22
S13	166	S8 and S10	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:41
S14	111	S13 and S7	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:47
S15	29	"uric acid lowering"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/01 14:42
S16	6221	"uric acid"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:55
S17	716	S8 and S16	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 10:59
S18	1808284	decreasing or reductiin or reduction or lowering	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 11:00
S19	2668056	decreasing or reducing or reduction or lowering	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 11:01
S20	3888	S16 and S19	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 11:01
S21	595	S20 and S8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 11:03
S22	40	"uric acid reducing" or "uric acid lowering"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 11:08
S23	4	S22 and S8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/25 11:08

S24	3867	allopurinol or carprofen	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/28 10:49
S25	470	"xanthine oxidase inhibitor"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/28 10:50
S26	260	S24 and S25	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/28 10:50
S27	48671	hypertension	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/28 11:05
S28	111	S26 and S27	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/03/28 11:05

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                   (ROSPATENT) added to list of core patent offices covered
 NEWS  4  FEB 28   PATDPAFULL - New display fields provide for legal status
                   data from INPADOC
 NEWS  5  FEB 28   BABS - Current-awareness alerts (SDIs) available
 NEWS  6  FEB 28   MEDLINE/LMEDLINE reloaded
 NEWS  7  MAR 02   GBFULL: New full-text patent database on STN
 NEWS  8  MAR 03   REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  9  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  10 MAR 22   KOREAPAT now updated monthly; patent information enhanced
 NEWS  11 MAR 22   Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  12 MAR 22   PATDPASPC - New patent database available
 NEWS  13 MAR 22   REGISTRY/ZREGISTRY enhanced with experimental property tags

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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FILE 'MEDLINE' ENTERED AT 13:28:43 ON 01 APR 2005

=> s xanthine oxidase inhibitor?
L1 1214 XANTHINE OXIDASE INHIBITOR?

=> s xanthine oxidase inhibitor
L2 1166 XANTHINE OXIDASE INHIBITOR

=> s hypertension
L3 306913 HYPERTENSION

=> s L1 and L3
L4 40 L1 AND L3

=> d 1-40 ibib abs

L4 ANSWER 1 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:304720 CAPLUS
DOCUMENT NUMBER: 141:306755
TITLE: Uric acid: role in cardiovascular disease and effects of losartan
AUTHOR(S): Alderman, Michael; Aiyer, Kala J. V.
CORPORATE SOURCE: Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA
SOURCE: Current Medical Research and Opinion (2004), 20(3), 369-379
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. A substantial body of epidemiol. and exptl. evidence suggests that serum uric acid is an important, independent risk factor for cardiovascular and renal disease especially in patients with **hypertension**, heart failure, or diabetes. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients with diabetes. Further, patients with **hypertension** and hyperuricemia have a 3- to 5-fold increased risk of experiencing coronary artery disease or cerebrovascular disease compared with patients with normal uric acid levels. Although the mechanisms by which uric acid may play a pathogenetic role in cardiovascular disease is unclear, hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheol., and aggregation. **Xanthine oxidase inhibitors** (e.g., allopurinol) or a variety of uricosuric agents (e.g., probenecid, sulfinpyrazone, benzbromarone, and benziodarone) can lower elevated uric acid levels but it is unknown whether these agents reversibly impact cardiovascular outcomes. However, the findings of the recent LIFE study in patients with **hypertension** and left ventricular hypertrophy suggest the possibility that a treatment-induced decrease in serum uric acid may indeed attenuate cardiovascular risk. LIFE showed that approx. 29% (14% to 107%, p = 0.004) of the treatment benefit of a losartan-based vs. atenolol-based therapy on the primary composite endpoint (death, myocardial infarction, or stroke) may be ascribed to differences in achieved serum uric acid levels. Overall, serum uric acid may be a powerful tool to help stratify risk for cardiovascular disease. At the very least, it should be carefully considered when evaluating overall cardiovascular risk.
REFERENCE COUNT: 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:295980 CAPLUS
DOCUMENT NUMBER: 141:325356
TITLE: Inhibitory influences of **xanthine**

oxidase inhibitor and angiotensin I-converting enzyme inhibitor on multinucleated giant cell formation from monocytes by down-regulation of adhesion molecules and purinergic receptors

AUTHOR(S): Mizuno, K.; Okamoto, H.; Horio, T.

CORPORATE SOURCE: Department of Dermatology, Kansai Medical University, Moriguchi, Osaka, 570-8507, Japan

SOURCE: British Journal of Dermatology (2004), 150(2), 205-210
CODEN: BJDEAZ; ISSN: 0007-0963

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Allopurinol, a **xanthine oxidase inhibitor**, and captopril, an inhibitor of angiotensin I-converting enzyme, are widely used for hyperuricemia and **hypertension**, resp. There have been reported cases showing that these two agents are effective for the treatment of granulomatous diseases such as sarcoidosis, although the mode of action is not elucidated. Objectives: We examined the in vitro effects of these agents on the formation of multinucleated giant cells (MGC) from human monocytes by Con A-stimulated mononuclear cell supernatants (conditioned medium). Methods: We cultured monocytes with conditioned medium and each agent and compared the rate of MGC formation as well as the expression of adhesion mols. and P2X7 receptor, which are involved in MGC formation. Results: The addition of 25 or 100 μg mL-1 allopurinol or 0.125-1.0 μg mL-1 captopril inhibited MGC formation. Monocytes treated with these agents exhibited less expression of intercellular adhesion mol.-1 (ICAM-1) than untreated monocytes. The susceptibility of monocytes cultured in conditioned medium for 24 h to 2'-and 3'-o-(4-benzoyl-benzoyl)ATP-mediated cytolysis was significantly lower in monocytes treated with these agents than in untreated monocytes. Conclusions: Allopurinol and captopril have a therapeutic effect on granulomatous disorders by a direct action on monocyte/macrophage lineage cells partly through down-regulation of ICAM-1 and P2X7 receptor.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:991488 CAPLUS

DOCUMENT NUMBER: 140:27834

TITLE: Preparation of pyridazinyloximes as phosphodiesterase IV inhibitors.

INVENTOR(S): Eggenweiler, Hans-Michael; Beier, Norbert; Schelling, Pierre; Wolf, Michael

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104205	A1	20031218	WO 2003-EP5173	20030516
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10225574	A1	20031218	DE 2002-10225574	20020610

BR 2003011311	A	20050215	BR 2003-11311	20030516
EP 1511737	A1	20050309	EP 2003-732395	20030516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			DE 2002-10225574	A 20020610
			WO 2003-EP5173	W 20030516

OTHER SOURCE(S): MARPAT 140:27834

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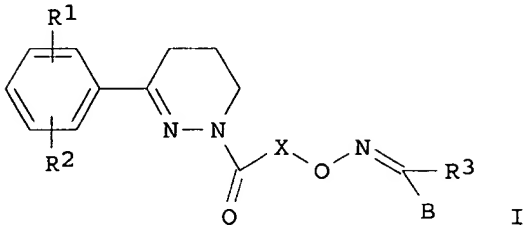

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AB Title compds. [I; R1, R2 = H, OH, OR8, SR8, SOR8, SO2R8, halo; R1R2 = OCH2O, OCH2CH2O; R3 = H, AR7, COAR7, CO2AR7, CONH2, NH2, etc.; R7 = H, CO2H, NH2, OH, etc.; R8 = (substituted) alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, etc.; A = null, (O, S, SO, SO2, imino-interrupted) alkylene, alkenylene, cycloalkylene; B = (substituted) aryl, heteroaryl; X = (O, S, SO, SO2, imino-interrupted) alkylene], were prepared as phosphodiesterase IV inhibitors for treating osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases and AIDS (no data). Thus, 3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine was treated sequentially with chloroacetyl chloride, N-hydroxyphthalimide, ethanolamine, and 4-methoxybenzaldehyde to give 4-methoxybenzaldehyde O-[2-[3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-2-oxoethyl]oxime.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:356269 CAPLUS
DOCUMENT NUMBER: 138:348761
TITLE: Type 4 phosphodiesterase inhibitors and therapeutic uses thereof
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037349	A1	20030508	WO 2002-EP9596	20020828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,				

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1463509 A1 20041006 EP 2002-802281 20020828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
US 2004259863 A1 20041223 US 2004-494379 20040430
PRIORITY APPLN. INFO.: EP 2001-125394 A 20011031
WO 2002-EP9596 W 20020828
OTHER SOURCE(S): MARPAT 138:348761
AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:328016 CAPLUS
DOCUMENT NUMBER: 138:366815
TITLE: Endothelin-1 increases vascular superoxide via endothelinA-NADPH oxidase pathway in low-renin **hypertension**
AUTHOR(S): Li, Lixin; Fink, Gregory D.; Watts, Stephanie W.; Northcott, Carrie A.; Galligan, James J.; Pagano, Patrick J.; Chen, Alex F.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, USA
SOURCE: Circulation (2003), 107(7), 1053-1058
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiotensin II-induced **hypertension** is associated with NAD(P)H oxidase-dependent superoxide production in the vessel wall. Vascular superoxide level is also increased in deoxycorticosterone acetate (DOCA)-salt **hypertension**, which is associated with a markedly depressed plasma renin activity because of sodium retention. However, the mechanisms underlying superoxide production in low-renin **hypertension** are undefined. This study investigated (1) whether and how endothelin-1 (ET-1), which is increased in DOCA-salt hypertensive rats, contributes to arterial superoxide generation and (2) the effect of gene transfer of manganese superoxide dismutase and endothelial nitric oxide synthase. Both superoxide and ET-1 levels were significantly elevated in carotid arteries of DOCA-salt rats compared with that of the sham-operated controls. ET-1 concentration-dependently stimulated superoxide production in vitro in carotid arteries of normotensive rats. The increase in arterial superoxide in both ET-1-treated normotensive and DOCA-salt rats was reversed by a selective ETA receptor antagonist, ABT-627, the flavoprotein inhibitor diphenyleneiodonium, and the NADPH oxidase inhibitor apocynin but not by the nitric oxide synthase inhibitor Nω-L-arginine Me ester or the **xanthine oxidase inhibitor** allopurinol. Furthermore, in vivo blockade of ETA receptors significantly reduced arterial superoxide levels, with a concomitant decrease of systolic blood pressure in DOCA-salt rats. Ex vivo gene transfer of manganese superoxide dismutase or endothelial nitric oxide synthase also suppressed superoxide levels in carotid arteries of DOCA-salt rats. These findings suggest that ET-1 augments vascular superoxide production at least in part via an ETA/NADPH oxidase pathway in low-renin mineralocorticoid **hypertension.**
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:870447 CAPLUS
DOCUMENT NUMBER: 138:236192
TITLE: A Role for Uric Acid in the Progression of Renal

Disease
AUTHOR(S): Kang, Duk-Hee; Nakagawa, Takahiko; Feng, Lili; Watanabe, Susumu; Han, Lin; Mazzali, Marilda; Truong, Luan; Harris, Raymond; Johnson, Richard J.
CORPORATE SOURCE: Division of Nephrology, Baylor College of Medicine, Houston, Texas, USA
SOURCE: Journal of the American Society of Nephrology (2002), 13(12), 2888-2897
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hyperuricemia is associated with renal disease, but it is usually considered a marker of renal dysfunction rather than a risk factor for progression. Recent studies have reported that mild hyperuricemia in normal rats induced by the uricase inhibitor, oxonic acid (OA), results in **hypertension**, intrarenal vascular disease, and renal injury. This led to the hypothesis that uric acid may contribute to progressive renal disease. To examine the effect of hyperuricemia on renal disease progression, rats were fed 2% OA for 6 wk after 5/6 remnant kidney (RK) surgery with or without the **xanthine oxidase inhibitor**, allopurinol, or the uricosuric agent, benziodarone. Renal function and histol. studies were performed at 6 wk. Given observations that uric acid induces vascular disease, the effect of uric acid on vascular smooth muscle cells in culture was also examined RK rats developed transient hyperuricemia (2.7 mg/dL at week 2), but then levels returned to baseline by week 6 (1.4 mg/dL). In contrast, RK+OA rats developed higher and more persistent hyperuricemia (6 wk, 3.2 mg/dL). Hyperuricemic rats demonstrated higher BP, greater proteinuria, and higher serum creatinine than RK rats. Hyperuricemic RK rats had more renal hypertrophy and greater glomerulosclerosis (24.2 ± 2.5 vs. 17.5 ± 3.4%; $P < 0.05$) and interstitial fibrosis (1.89 ± 0.45 vs. 1.52 ± 0.47; $P < 0.05$). Hyperuricemic rats developed vascular disease consisting of thickening of the preglomerular arteries with smooth muscle cell proliferation; these changes were significantly more severe than a historical RK group with similar BP. Allopurinol significantly reduced uric acid levels and blocked the renal functional and histol. changes. Benziodarone reduced uric acid levels less effectively and only partially improved BP and renal function, with minimal effect on the vascular changes. To better understand the mechanism for the vascular disease, the expression of COX-2 and renin were examined Hyperuricemic rats showed increased renal renin and COX-2 expression, the latter especially in preglomerular arterial vessels. In in vitro studies, cultured vascular smooth muscle cells incubated with uric acid also generated COX-2 with time-dependent proliferation, which was prevented by either a COX-2 or TXA-2 receptor inhibitor. Hyperuricemia accelerates renal progression in the RK model via a mechanism linked to high systemic BP and COX-2-mediated, thromboxane-induced vascular disease. These studies provide direct evidence that uric acid may be a true mediator of renal disease and progression.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:673856 CAPLUS
DOCUMENT NUMBER: 138:214866
TITLE: 2-Styrylchromones as novel inhibitors of xanthine oxidase. A structure-activity study
AUTHOR(S): Fernandes, Eduarda; Carvalho, Felix; Silva, Artur M. S.; Santos, Clementina M. M.; Pinto, Diana C. G. A.; Cavaleiro, Jose A. S.; De Lourdes Bastos, Maria
CORPORATE SOURCE: ICETA/CEQUP, Toxicology Department, Faculty of Pharmacy, University of Porto-Rua Anibal Cunha, Oporto, 4050-047, Port.
SOURCE: Journal of Enzyme Inhibition and Medicinal Chemistry

(2002), 17(1), 45-48
CODEN: JEIMAZ; ISSN: 1475-6366
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was the evaluation of the xanthine oxidase (XO) inhibition produced by some synthetic 2-styrylchromones. Ten polyhydroxylated derivs. with several substitution patterns were synthesized, and these and a pos. control, allopurinol, were tested for their effects on XO activity by measuring the formation of uric acid from xanthine. The synthesized 2-styrylchromones inhibited xanthine oxidase in a concentration-dependent and non-competitive manner. Some IC50 values found were as low as 0.55 μM, which, by comparison with the IC50 found for allopurinol (5.43 μM), indicates promising new inhibitors. Those 2-styrylchromones found to be potent XO inhibitors should be further evaluated as potential agents for the treatment of pathologies related to the enzyme's activity, as is the case of gout, ischemia/reperfusion damage, hypertension, hepatitis and cancer.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:594822 CAPLUS
DOCUMENT NUMBER: 137:154857
TITLE: Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060875	A1	20020808	WO 2001-IB2341	20011206
WO 2002060875	C1	20030731		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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CA 2436535	AA	20020808	CA 2001-2436535	20011206
EP 1355884	A1	20031029	EP 2001-273556	20011206
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EE 200300360	A	20031215	EE 2003-360	20011206
BR 2001016852	A	20040225	BR 2001-16852	20011206
JP 2004520386	T2	20040708	JP 2002-561026	20011206
NZ 526453	A	20050128	NZ 2001-526453	20011206
US 2002193612	A1	20021219	US 2002-62813	20020131
US 6649633	B2	20031118		
ZA 2003004894	A	20040624	ZA 2003-4894	20030624
US 2004048903	A1	20040311	US 2003-613988	20030702
BG 108038	A	20040730	BG 2003-108038	20030728
NO 2003003397	A	20030919	NO 2003-3397	20030730
PRIORITY APPLN. INFO.:			US 2001-265492P	P 20010131

WO 2001-IB2341 W 20011206
US 2002-62813 A3 20020131

OTHER SOURCE(S): MARPAT 137:154857
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

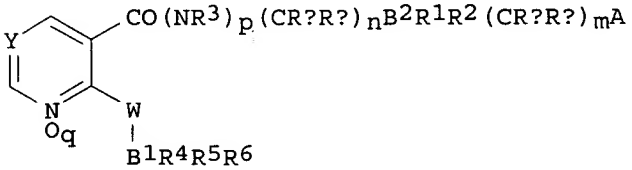
AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = O, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepared E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 μM to 20.0 μM in whole blood assay for LTE4.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:591707 CAPLUS
DOCUMENT NUMBER: 137:140509
TITLE: Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 180 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 1229034	A1	20020807	EP 2002-250202		20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
CA 2369462	AA	20020731	CA 2002-2369462		20020129
US 2002111495	A1	20020815	US 2002-62811		20020131
BR 2002000250	A	20021008	BR 2002-250		20020131
US 2004171798	A1	20040902	US 2004-781062		20040217
PRIORITY APPLN. INFO.:			US 2001-265240P	P	20010131
			US 1997-43403P	P	19970404
			US 1998-105120P	P	19981021
			US 2002-62811	B1	20020131

OTHER SOURCE(S): MARPAT 137:140509
GI



I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepared (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aqueous NaOH was added to the suspension, and the reaction mixture was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:161639 CAPLUS
DOCUMENT NUMBER: 136:338671
TITLE: In vivo evidence for antioxidant potential of estrogen in microvessels of female spontaneously hypertensive rats
AUTHOR(S): Dantas, Ana Paula V.; Tostes, Rita C. A.; Fortes, Zuleica B.; Costa, Sonia G.; Nigro, Dorothy; Carvalho, Maria Helena C.
CORPORATE SOURCE: Laboratory of Hypertension, Department of Pharmacology, Institute of Biomedical Science, University of Sao Paulo, Brazil
SOURCE: Hypertension (2002), 39(2, Pt. 2), 405-411
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In studies conducted in vitro, it has been demonstrated that estrogen has an antioxidant potential that may contribute to its protective effects on the cardiovascular system. However, the antioxidant effect of estrogen in vivo has not been demonstrated. To address this issue, in this study the effects of estrogen on oxidative stress were evaluated in microvessels studied in vivo. Oxidative stress was evaluated by using intravital microscopy in mesenteric arterioles from female spontaneously hypertensive rats (SHR) in physiol. estrous (OE), ovariectomized (OVX), OVX treated with estradiol (E2), or estradiol + progesterone (E/P). The mesenteries were superfused with hydroethidine. a reduced and nonfluorescent precursor of ethidium bromide (EB). In the presence of reactive oxygen species, hydroethidine is transformed intracellularly in EB, which binds to DNA and can be detected by its red fluorescence. The percentage of EB-pos. nuclei along the arteriolar wall in OVX (28.4±4.3) was significantly increased compared with OE (14.2±3.9; P<0.05). The OVX overprodn. of oxyradicals was attenuated by E2 (15.7±2.2) and E/P (14.8±0.8). Treatment with the superoxide dismutase mimetic MnTMPyP attenuated by 75% the oxidation of hydroethidine in both OE and OVX. Conversely. mannitol, that decomps. hydroxyl radical, and L-NAME, a nitric oxide synthase inhibitor, had no significant effects on hydroethidine oxidation No differences on hydrogen peroxide plasma concentration were observed among the groups, suggesting that superoxide anion is the most likely oxyradical involved in the increased oxidative stress observed in OVX. The treatment of mesenteries with diphenyleneiodonium (DPI), an NADP (NADPH)-oxidase inhibitor, but not with oxypurinol, a **xanthine-oxidase inhibitor**, produced a significant reduction of oxyradical generation in OVX microvessels and a slight decrease in those from OE. Chronic treatment of female SHR with losartan caused similar decreases in oxyradicals in both OE and OVX,

whereas diclofenac and verapamil had no effects. Together these data suggest that estrogen reduces superoxide anion bioavailability in vivo. The antioxidant effect of estrogen, which can contribute to a less pronounced endothelial dysfunction in female SHR, may be dependent on a direct modulatory action of estrogen on NADPH activity.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:136636 CAPLUS
DOCUMENT NUMBER: 137:70
TITLE: Reducing uric acid as a means to prevent cardiovascular and renal disease
AUTHOR(S): Watanabe, Susumu; Kanellis, John; Nakagawa, Takahiko; Han, Lin; Ohashi, Ryuji; Lan, Hui; Feng, Lili; Johnson, Richard J.
CORPORATE SOURCE: Div. of Nephrology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(2), 193-199
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Hyperuricemia (uric acid levels > 6.5 mg/dL in men and > 6.0 mg/dL in women) affects .apprx. 10% of the population but is not classically treated with uric acid-lowering drugs unless there is a history of gout or uric acid renal stones. However, there is strong epidemiol. evidence that hyperuricemia is associated with cardiovascular and renal disease. It has recently been shown that mild hyperuricemia in rats causes **hypertension**, vascular disease and renal injury and that lowering uric acid levels can prevent these complications. Thus, there is renewed interest in current and future therapies that may be used to lower uric acid. This paper reviews current therapies, particularly the **xanthine oxidase inhibitors** and uricosuric agents, as well as novel approaches to uric acid reduction, such as replacement enzyme therapies.

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:10270 CAPLUS
DOCUMENT NUMBER: 136:64126
TITLE: Agent reducing uric acid levels for treatment of cardiovascular disease and hypertension
INVENTOR(S): Kivlighn, Salah; Johnson, Richard J.; Mazzali, Marilda
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; University of Washington
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000210	A2	20020103	WO 2001-US20457	20010628
WO 2002000210	A3	20021024		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2413201	AA	20020103	CA 2001-2413201		20010628
US 2002019360	A1	20020214	US 2001-892505		20010628
EP 1317258	A2	20030611	EP 2001-946722		20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004517804	T2	20040617	JP 2002-504992		20010628
PRIORITY APPLN. INFO.:			US 2000-214825P	P	20000628
			WO 2001-US20457	W	20010628

AB This invention relates to a method for treating and preventing **hypertension** by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Addnl., the scope of the invention includes a method of treating coronary heart disease by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Allopurinol administered from the initiation of an oxonic acid diet prevented the development of hyperuricemia and **hypertension.** In hypertensive, hyperuricemic rats, either withdrawal of the oxonic acid or adding allopurinol also resulted in a reduction in the blood pressure in association with a fall in serum uric acid values.

L4 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2001:887837 CAPLUS
DOCUMENT NUMBER:	136:148868
TITLE:	NADH/NADPH oxidase and enhanced superoxide production in the mineralocorticoid hypertensive rat
AUTHOR(S):	Beswick, Richard A.; Dorrance, Anne M.; Leite, Romulo; Webb, R. Clinton
CORPORATE SOURCE:	Department of Physiology, University of Michigan, Ann Arbor, MI, USA
SOURCE:	Hypertension (2001), 38(5), 1107-1111 CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB We previously reported increased aortic reactive oxygen species (ROS) production in mineralocorticoid (deoxycorticosterone acetate [DOCA]-salt) hypertensive rats. In the present study, we tested the hypothesis that NADH/NADPH oxidase is responsible for increased ROS production, namely superoxide (O2-), in aorta from the DOCA-salt rat. Treatment of aortic rings from DOCA-salt rats with the NO synthase inhibitor N-nitro-L-arginine and the xanthine oxidase **inhibitor** allopurinol did not significantly change O2- production Furthermore, de-endothelialization of aorta from DOCA-salt rats did not affect O2- production compared with that of sham-operated rats. Thus, xanthine oxidase and uncoupled endothelial NO synthase were not responsible for increased O2- production in the DOCA-salt rats. In contrast, treatment with the NADPH oxidase inhibitor apocynin significantly decreased O2- production in aortic rings from DOCA-salt rats compared with sham-operated rats. Moreover, long-term administration of apocynin (in drinking water, 1.5 mmol/L, 28 days) to DOCA-salt rats significantly decreased systolic blood pressure compared with that of rats treated with DOCA-salt alone. Furthermore, O2- production in aortic rings from DOCA-salt rats treated with apocynin for 28 days was reduced compared with that of untreated DOCA-salt rats. Reverse transcriptase-polymerase chain reaction (RT-PCR) anal. demonstrated that DOCA-salt rats have significantly greater mRNA levels of the NADPH oxidase subunit p22phox than do sham-operated rats. These findings suggest that NADPH oxidase is increased and is responsible for increased O2- production and possibly contributes to increased blood pressure in the DOCA-salt hypertensive rat.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:887836 CAPLUS
DOCUMENT NUMBER: 136:148867
TITLE: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism
AUTHOR(S): Mazzali, Marilda; Hughes, Jeremy; Kim, Yoon-Goo; Jefferson, J. Ashley; Kang, Duk-Hee; Gordon, Katherine L.; Lan, Hui Y.; Kivlighn, Salah; Johnson, Richard J.
CORPORATE SOURCE: Division of Nephrology, University of Washington Medical Center, Seattle, WA, USA
SOURCE: Hypertension (2001), 38(5), 1101-1106
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An elevation in circulating serum uric acid is strongly associated with the development of **hypertension** and renal disease, but whether uric acid has a causal role or whether it simply indicates patients at risk for these complications remains controversial. We tested the hypothesis that uric acid may have a causal role in the development of **hypertension** and renal disease by examining the effects of mild hyperuricemia in rats. Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 wk, whereas control rats remained normotensive. The development of **hypertension** was prevented by concurrent treatment with either a **xanthine oxidase inhibitor** (allopurinol) or a uricosuric agent (benziodarone), both of which lowered uric acid levels. Blood pressure could also be lowered by reducing uric acid levels with either allopurinol or oxonic acid withdrawal. A direct relationship was found between blood pressure and uric acid (r=0.75, n=69), with a 10-mm Hg blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid. The kidneys were devoid of urate crystals and were normal by light microscopy. However, immunohistochem. stains documented an ischemic type of injury with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin. Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal NO synthase. Both the renal injury and **hypertension** were reduced by treatment with enalapril or L-arginine. In conclusion, mild hyperuricemia causes **hypertension** and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:861482 CAPLUS
DOCUMENT NUMBER: 134:32977
TITLE: Methods and compositions for the treatment of neuroleptic and related disorders using sertindole derivatives
INVENTOR(S): Jerussi, Thomas P.
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072837	A2	20001207	WO 2000-US14984	20000531

WO 2000072837 A3 20010517
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 6489341 B1 20021203 US 2000-580492 20000530
PRIORITY APPLN. INFO.: US 1999-137447P P 19990602
US 2000-580492 A 20000530

AB The invention relates to novel methods using, and pharmaceutical compns. and dosage forms comprising, sertindole derivs. Sertindole derivs. include, but are not limited to, nor-sertindole, 5-oxo-sertindole, dehydro-sertindole, and dehydro-nor-sertindole. The methods of the invention are directed to the treatment and prevention of neuroleptic and related disorders such as, but are not limited to, psychotic disorders, depression, anxiety, substance addiction, memory impairment and pain. For example, capsules were prepared containing a sertindole derivative 50.0 mg, lactose 48.5 mg, TiO2 0.5 mg, and Mg stearate 1.0 mg.

L4 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:259979 CAPLUS
DOCUMENT NUMBER: 132:288794
TITLE: Sympathetic nervous system activity-reducing agents for treatment of disease- or age-related weight loss and for enhancement of exercise performance
INVENTOR(S): Anker, Stefan Dietmar; Coats, Andrew Justin Stewart
PATENT ASSIGNEE(S): Imperial College Innovations Limited, UK
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021509	A2	20000420	WO 1999-GB3302	19991015
WO 2000021509	A3	20001109		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1121111	A2	20010808	EP 1999-947762	19991015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002527378	T2	20020827	JP 2000-575485	19991015
PRIORITY APPLN. INFO.:			GB 1998-22458 A	19981015
			GB 1998-22459 A	19981015
			GB 1999-17181 A	19990723
			WO 1999-GB3302 W	19991015

AB A method of treating weight loss due to underlying disease in a patient, the method comprising administering to the patient an effective amount of an agent which reduces sympathetic nervous system activity. A method of treating weight loss due to underlying disease in a patient, the method comprising administering to the patient an effective amount of any one or more of the following: a compound which inhibits the effect of aldosterone such as an aldosterone antagonist; a chymase inhibitor; a cathepsin B inhibitor; a β receptor blocker; an imidazoline receptor antagonist; a centrally acting α receptor antagonist; a peripherally acting α receptor antagonist; a ganglion blocking agent; a drug that has an effect on cardiovascular reflexes and thereby reduces SNS activity such as

an opiate; scopolamine; an endothelin receptor antagonist; and a **xanthine oxidase inhibitor.** The methods are particularly useful in treating cardiac cachexia. The sympathetic nervous system activity-reducing agents may also be used to treat weight loss due to aging and to enhance exercise performance.

L4 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:229952 CAPLUS
DOCUMENT NUMBER: 132:260495
TITLE: Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild **hypertension**
AUTHOR(S): Butler, Robert; Morris, Andrew D.; Belch, Jill J. F.; Hill, Alexander; Struthers, Allan D.
CORPORATE SOURCE: University Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
SOURCE: Hypertension (2000), 35(3), 746-751
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Therapeutic strategies against free radicals have mostly focused on the augmentation of antioxidant defenses (eg, vitamins C and E). A novel approach is to prevent free radical generation by the enzyme system xanthine oxidase. We examined whether the inhibition of xanthine oxidase with allopurinol can improve endothelial function in subjects with type 2 diabetes and coexisting mild **hypertension** compared with control subjects of a similar age. We examined 23 subjects (11 patients with type 2 diabetes and 12 healthy age-matched control subjects) in 2 parallel groups. The subjects were administered 300 mg allopurinol in a randomized, placebo-controlled study in which both therapies were administered for 1 mo. Endothelial function was assessed with bilateral venous occlusion plethysmog., in which the forearm blood flow responses to intra-arterial infusions of endothelium-dependent and -independent vasodilators were measured. Allopurinol significantly increased the mean forearm blood flow response to acetylcholine by 30% (3.16±1.21 vs. 2.54±0.76 mL · 100 mL-1 · min-1 allopurinol vs. placebo; P=0.012, 95% CI 0.14, 1.30) but did not affect the nitroprusside response in patients with type 2 diabetes. There was no significant impact on either endothelium-dependent or -independent vascular responses in age-matched control subjects. Allopurinol improved endothelial function to near-normal levels. Regarding markers of free radical activity, the level of malondialdehyde was significantly reduced (0.30±0.04 vs. 0.34±0.05 μmol/L for allopurinol vs. placebo, P=0.03) in patients with type 2 diabetes but not in control subjects. The xanthine **oxidase inhibitor** allopurinol improves endothelial dysfunction in patients with type 2 diabetes with mild **hypertension** but not in matched control subjects. In the former group, allopurinol restored endothelial function to near-normal levels.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:231552 CAPLUS
DOCUMENT NUMBER: 130:249107
TITLE: System and method for measuring hydrogen peroxide levels in a fluid and method for assessing oxidative stress
INVENTOR(S): Lacy, Fred; Schmid-Schonbein, Geert W.; Gough, David
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9915891	A1	19990401	WO 1998-US19013	19980914
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9894805	A1	19990412	AU 1998-94805	19980914
PRIORITY APPLN. INFO.:			US 1997-60010P	P 19970925
			WO 1998-US19013	W 19980914

AB The detection system includes a pair of electrochem. hydrogen peroxide sensors, each sensor having working, counter and reference electrodes. A bias voltage is applied to maintain a voltage difference between the working and reference electrodes. A sample aliquot of fluid was treated with either sodium azide or catalase. The sensors are placed in containers containing sufficient amts. of treated fluid to cover the active portions of the electrodes. The output current of each sensor is amplified, and the resulting amplified signals are combined and subtracted to provide a signal which is representative of the level of hydrogen peroxide in the fluid. In a method for assessing oxidative stress, including that related to essential **hypertension**, the detection system is used to determine a representative level of hydrogen peroxide in blood plasma drawn from a test subject. The level of hydrogen peroxide is directly related to the level of reactive oxygen species in the plasma, and can be used as an accurate predictor of risk for essential **hypertension** or other conditions related to oxidative stress. Blood plasma samples of normotensive subjects and patients with essential **hypertension** were analyzed by the system. When hypertensives were compared with family history neg. normotensives, it was found that the hypertensive group had a higher mean arterial pressure by 23% as well as higher levels of plasma hydrogen peroxide by 48% over the normotensive control.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:350193 CAPLUS

DOCUMENT NUMBER: 129:93348

TITLE: Nitric oxide exposure inhibits endothelial NOS activity but not gene expression: a role for superoxide

AUTHOR(S): Sheehy, A. Macduff; Burson, Michael A.; Black, Stephen M.

CORPORATE SOURCE: Department of Pediatrics, University of California, San Francisco, CA, 94143-0106, USA

SOURCE: American Journal of Physiology (1998), 274(5, Pt. 1), L833-L841
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent studies have characterized a rebound pulmonary vasoconstriction with abrupt withdrawal of inhaled nitric oxide (NO) during therapy for pulmonary **hypertension**, suggesting that inhaled NO may downregulate basal NO production However, the exact mechanism of this rebound pulmonary **hypertension** remains unclear. The objectives of these studies were to determine the effect of NO exposure on endothelial NO synthase (eNOS) gene expression, enzyme activity, and posttranslational modification in cultured pulmonary arterial endothelial cells. Sodium nitroprusside (SNP) treatment had no effect on eNOS mRNA or protein levels

but did produce a significant decrease in enzyme activity. Furthermore, although SNP treatment induced protein kinase C (PKC)-dependent eNOS phosphorylation, blockade of PKC activity did not protect against the effects of SNP. When the **xanthine oxidase inhibitor** allopurinol or the superoxide scavenger 4,5-dihydroxy-1-benzene-disulfonic acid were co-incubated with SNP, the inhibitory effects on eNOS activity could be partially alleviated. Also, the levels of superoxide were found to be elevated 4.5-fold when cultured pulmonary arterial endothelial cells were exposed to the NO donor spermine/NO. This suggests that NO can stimulate xanthine oxidase to cause an increase in cellular superoxide generation. A reaction between NO and superoxide would produce peroxynitrite, which could then react with the eNOS protein, resulting in enzyme inactivation. This mechanism may explain, at least in part, how NO produces NOS inhibition in vivo and may delineate, in part, the mechanism of rebound pulmonary **hypertension** after withdrawal of inhaled NO.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:524796 CAPLUS
DOCUMENT NUMBER: 127:171328
TITLE: Xanthine oxidase inhibition with oxypurinol improves endothelial vasodilator function in hypercholesterolemic but not in hypertensive patients
AUTHOR(S): Cardillo, Carmine; Kilcoyne, Crescence M.; Cannon, Richard O., III; Quyyumi, Arshed A.; Panza, Julio A.
CORPORATE SOURCE: Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, 20892-1650, USA
SOURCE: Hypertension (Dallas) (1997), 30(1, Pt. 1), 57-63
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypercholesterolemic and hypertensive patients have impaired endothelium-dependent vasorelaxation because of decreased nitric oxide activity, but the mechanism underlying this abnormality is unknown. This study sought to determine whether an increased breakdown of nitric oxide by xanthine oxidase-generated superoxide anions could participate in these forms of endothelial dysfunction. We studied vascular responses to intrabrachial infusion of acetylcholine (an endothelium-dependent vasodilator, 7.5 to 30 μg/min) and sodium nitroprusside (a direct smooth muscle dilator, 0.8 to 3.2 μg/min) by strain-gauge plethysmog. before and during the combined administration of oxypurinol (300 μg/min), a **xanthine oxidase inhibitor**, in 20 hypercholesterolemic patients, 20 essential hypertensive patients, and 20 normal subjects. The vasodilator response to acetylcholine was blunted in hypercholesterolemic (highest flow, 8.2±8 mL · min-1 · dL-1) and hypertensive (8.5±4 mL · min-1 · dL-1) patients compared with control subjects (13.8±6.6 mL · min-1 · dL-1) (both P<.001); however, no differences were observed in the response to sodium nitroprusside. Oxypurinol did not change the response to acetylcholine in control subject (P=.26) and improved, but did not normalize, its vasodilator effect in hypercholesterolemic patients (P<.01). Oxypurinol did not affect the response to acetylcholine in hypertensive patients (P=.34) and did not modify the response to sodium nitroprusside in any group. These results suggest that xanthine oxidase-generated superoxide anions are partly responsible for the impaired endothelial vasodilator function of hypercholesterolemic patients. In contrast, this mechanism does not appear to play a significant role in essential **hypertension.**

L4 ANSWER 21 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:207673 CAPLUS

DOCUMENT NUMBER: 124:313438
TITLE: Potentiation of nitric oxide-mediated vasorelaxation by **xanthine oxidase inhibitors**
AUTHOR(S): Miyamoto, Yoichi; Akaike, Takaaki; Yoshida, Masaki; Goto, Shingo; Horie, Hidechika; Maeda, Hiroshi
CORPORATE SOURCE: School Medicine, Kumamoto Univ., Kumamoto, 860, Japan
SOURCE: Proceedings of the Society for Experimental Biology and Medicine (1996), 211(4), 366-73
CODEN: PSEBAA; ISSN: 0037-9727
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitric oxide (NO), now almost synonymous with endothelium-derived relaxing factor (EDRF), reacts with superoxide anion radical (O2-) and forms a potentially toxic mol. species, peroxynitrite (ONOO-). Because xanthine oxidase (XO) seems to be a major O2--producing enzyme in the vascular system, it is important to clarify the mechanism of XO regulation of NO/EDRF. We first characterized the inhibition of XO in vitro by three types of pyrazolopyrimidine derivs. Kinetic studies indicated that 4-amino-6-hydroxypyrazolo[3,4-d]pyrimidine (AHPP) and allopurinol competitively inhibited the conversion of xanthine to uric acid catalyzed by XO, with apparent Ki values of 0.17 ± 0.02 and 0.50 ± 0.03 μM, resp.; alloxanthine inhibited this conversion in a noncompetitive manner with an apparent Ki value of 3.54 ± 1.12 μM. O2- generation in the xanthine/XO system assayed by lucigenin-dependent chemiluminescence was suppressed most strongly by AHPP in a dose-dependent fashion; allopurinol itself appears to reduce the enzyme by transfer of an electron to O2, thus generating O2-. AHPP significantly augmented EDRF-mediated relaxation of aortic rings from both rabbits and spontaneously hypertensive rats (SHR) in a dose-dependent manner, whereas allopurinol did not affect the relaxation and only marginal potentiation of the vasorelaxation was observed with alloxanthine. Finally, i.v. injection of AHPP (50.4 mg/kg; 100 μmol/300 g rat) reduced the blood pressure of SHR rats to 70% of the initial pressure; this pressure is almost the blood pressure of normal rats. Allopurinol (100 μmol/300 g rat; i.v.) showed transient decrease in blood pressure and moderate reduction of **hypertension** of SHR (10%) was observed with i.v. injection of alloxanthine (100 μmol/300 g rat). On the basis of these results, it seems that XO regulates EDRF/NO. via production of O2-.

L4 ANSWER 22 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:624598 CAPLUS
DOCUMENT NUMBER: 123:80741
TITLE: In vivo evidence for microvascular oxidative stress in spontaneously hypertensive rats. Hydroethidine microfluorography
AUTHOR(S): Suzuki, Hidekazu; Swei, Allen; Zweifach, Benjamin W.; Schmid-Schonbein, Geert W.
CORPORATE SOURCE: Institute Biomedical Engineering, University California San Diego, La Jolla, CA, 92093-0412, USA
SOURCE: Hypertension (1995), 25(5), 1083-9
CODEN: HPRTDN; ISSN: 0194-911X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The factors that predispose to the accelerated organ injury that accompanies the hypertensive syndrome have remained speculative and without a firm exptl. basis. Indirect evidence has suggested that a key feature may be related to an enhanced oxygen radical production The purpose of this study was to refine and use a technique to visualize evidence of spontaneous microvascular oxidative stress in vivo in the spontaneously hypertensive rat (SHR) compared with its normotensive control, the Wistar-Kyoto rat (WKY). We investigated the effects of adrenal glucocorticoids on the microvascular oxidative stress sequence. The mesentery was superfused with hydroethidine, a reduced, nonfluorescent

precursor of ethidium bromide. In the presence of oxidative challenge, hydroethidine is transformed intracellularly into the fluorescent compound ethidium bromide, which binds to DNA and can be detected by virtue of its red fluorescence. The fluorescent light emission from freshly exteriorized and otherwise unstimulated mesentery microvessels was recorded by digital microscopy. The number of ethidium bromide-pos. nuclei along the arteriolar and venular walls in SHR was found to be significantly increased above the level exhibited by WKY. The elevation in ethidium bromide fluorescence in SHR arterioles could be attenuated by a synthetic glucocorticoid inhibitor and in rats subjected to adrenalectomy. The administration of glucocorticoids after adrenalectomy by injection of dexamethasone restored the oxidative reaction in SHR arterioles. Treatment with dimethylthiourea and with a **xanthine oxidase inhibitor** attenuated the superoxide formation. Although a nitric oxide synthase inhibitor (NG-nitro-L-arginine Me ester) enhanced the ethidium bromide staining in WKY, it did not affect that in SHR. Our findings suggest an enhancement of spontaneous oxidative stress in the microvascular wall of SHR that appears to be associated with glucocorticoid synthesis.

L4 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:309509 CAPLUS
DOCUMENT NUMBER: 122:71419
TITLE: Allopurinol fails to protect against gentamicin-induced renal damage in normotensive and spontaneously hypertensive rats
AUTHOR(S): Smyth, B.J.; Davis, W.G.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, SC, 29425-2645, USA
SOURCE: Nephron (1994), 68(4), 468-72
CODEN: NPRNAY; ISSN: 0028-2766
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent research suggests the involvement of hydroxyl and superoxide free radicals in the development of gentamicin-induced acute renal tubular necrosis. Xanthine oxidase has been implicated as an important source of superoxide free radicals. Spontaneously hypertensive (Wistar-Kyoto) rats (SHR) have excessive oxidant stress which may render them more sensitive to the reported oxygen free radical producing effects of gentamicin. This study was undertaken to determine if the **xanthine oxidase inhibitor** allopurinol will ameliorate the effects of gentamicin. Normotensive Wistar-Kyoto (WKY) rats and SHR were administered allopurinol (40 mg/kg twice daily) orally 4 days before and throughout a 12-day gentamicin treatment period. The allopurinol only treatment group demonstrated no noticeable histol. or functional changes considered to be indicative of nephrotoxicity. Gentamicin-injected WKY rats and SHR equally demonstrated extensive proximal tubular and glomerular damage characteristic of aminoglycoside-induced kidney damage. Allopurinol failed to protect either rat strain against the histol. damage caused by gentamicin. Equivalent alterations in serum creatinine, serum gentamicin, urinary N-acetyl-β-D-glucos-aminidase excretion, body weight, urinary output, and blood pressure occurred in the gentamicin with allopurinol and gentamicin only treatment groups. Our results demonstrate allopurinol does not ameliorate the pathogenesis of gentamicin-induced renal damage. SHR do not appear to be more sensitive to the effects of gentamicin-induced kidney damage with or without allopurinol as compared with WKY rats.

L4 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:420255 CAPLUS
DOCUMENT NUMBER: 119:20255
TITLE: Protective effects of therapy with a protease and **xanthine oxidase inhibitor** in short form pancreatic biliary obstruction and

ischemia in rats
AUTHOR(S): Hirano, Tetsuya; Manabe, Tadao; Steer, Michael; Printz, Hartmut; Calne, Roy; Tobe, Takayoshi
CORPORATE SOURCE: Dep. Surg., Addenbrookes Hosp., Cambridge, UK
SOURCE: Surgery, Gynecology and Obstetrics (1993), 176(4), 371-81
CODEN: SGOBA9; ISSN: 0039-6087.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The current study was done to evaluate the effects of short term (60 min) pancreatic biliary duct obstruction (PBDO) with intraductal **hypertension** (IDH) stimulated by secretin (0.2 clin. unit per kg per h) and caerulein (0.2 μg per kg per h) plus 30 min of temporary pancreatic ischemia (ISCH) produced by ligation of celiac and superior mesenteric artery on the exocrine pancreas and protective effects of a new potent protease inhibitor, ONO3307 in combination with **xanthine oxidase inhibitor**, allopurinol, in this multifactor related model of acute pancreatitis in rats. 12 H after PBDO with IDH plus ISCH, we observed hyperamylasemia; pancreatic edema into the pancreatic juice of rats stimulated by caerulein (control group-serum amylase levels, 6 ± 1 units per mL; pancreatic water content, 74 ± 1 percent. Furthermore, PBDO with IDH plus ISCH caused the redistribution of lysosomal enzyme from lysosomal fraction to zymogen fraction. Only PBDO with IDH caused no significant changes. Although only ONO3307 or allopurinol therapy showed the partial significant protective effects against pancreatic injuries, improving serum amylase levels, the administration of ONO3307 in combination therapy with allopurinol showed almost complete protective effects against the pancreatic injuries induced by PBDO with IDH plus ISCH (serum amylase levels, 9 ± 2 units per mL; pancreatic water content, 76 ± 2 percent; amylase and cathepsin B output, 7,127 ± 946 and 18 ± 3 units per kg per h; 1.3 kilo times gravity pellet, 28 ± 2 percent; 12 kilo times gravity pellet, 54 ± 2 percent, and energy charge equals 0.85 ± 0.02). These results indicate the important roles of temporary pancreatic ischemia and oxygen derived free radicals in the pathogenesis of pancreatic damages in this PBDO with IDH plus ISCH reperfusion in the rat model and the usefulness of combination therapy of such a new potent protease inhibitor and **xanthine oxidase inhibitor**, such as allopurinol, in the treatment of clin. acute pancreatitis.

L4 ANSWER 25 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:69302 CAPLUS
DOCUMENT NUMBER: 110:69302
TITLE: The malonyldialdehyde levels in the cerebral tissue after reperfusion following the occlusion of the bilateral common carotid artery in spontaneously hypertensive rats and the effect of allopurinol, a **xanthine oxidase inhibitor**
AUTHOR(S): Kawakami, Masato; Itoh, Toru; Tochigi, Shoichiro
CORPORATE SOURCE: Sch. Med., St. Marianna Univ., Japan
SOURCE: Nosotchu (1988), 10(5), 400-3
CODEN: NOSOD4; ISSN: 0912-0726
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Using spontaneously hypertensive rats, the authors studied the effect of allopurinol, a **xanthine oxidase inhibitor**, on lipid peroxidn. in the cerebral tissue after reperfusion for 30 min following the occlusion of the bilateral common carotid artery for 3 h. In the present study, the malonyldialdehyde (MDA) values were measured as indicators for lipid peroxides in the cerebral tissue, and compared them between the group pretreated with oral administrations of allopurinol (400 mg/kg) and the nontreated control group. As a result, the MDA value measured were found to be 68.9 nmol/gm in the Sham-operated group and 83.27 nmol/gm in the control group. However, the allopurinol-treated group showed a level as low as 67.62 nmol/gm which was significant

compared to that of the control group. These results suggest the possibility that allopurinol inhibits the lipid peroxidn. caused by the xanthine oxidase-linked free radical induced by cerebral ischemia and reperfusion.

L4 ANSWER 26 OF 40 MEDLINE on STN
ACCESSION NUMBER: 20041[illegible]59 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15025846
TITLE: Uric acid: role in cardiovascular disease and effects of losartan.
AUTHOR: Alderman Michael; Aiyer Kala J V
CORPORATE SOURCE: Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461-1602, USA.. alderman@aecom.yu.edu
SOURCE: Current medical research and opinion, (2004 Mar) 20 (3) 369-79. Ref: 93
Journal code: 0351014. ISSN: 0300-7995.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040318
Last Updated on STN: 20040611
Entered Medline: 20040610

AB A substantial body of epidemiological and experimental evidence suggests that serum uric acid is an important, independent risk factor for cardiovascular and renal disease especially in patients with **hypertension**, heart failure, or diabetes. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients with diabetes. Further, patients with **hypertension** and hyperuricemia have a 3- to 5-fold increased risk of experiencing coronary artery disease or cerebrovascular disease compared with patients with normal uric acid levels. Although the mechanisms by which uric acid may play a pathogenetic role in cardiovascular disease is unclear, hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, hemorheology, and aggregation. **Xanthine oxidase inhibitors** (e.g., allopurinol) or a variety of uricosuric agents (e.g., probenecid, sulfinpyrazone, benzbromarone, and benziodarone) can lower elevated uric acid levels but it is unknown whether these agents reversibly impact cardiovascular outcomes. However, the findings of the recent LIFE study in patients with **hypertension** and left ventricular hypertrophy suggest the possibility that a treatment-induced decrease in serum uric acid may indeed attenuate cardiovascular risk. LIFE showed that approximately 29% (14% to 107%, p = 0.004) of the treatment benefit of a losartan-based versus atenolol-based therapy on the primary composite endpoint (death, myocardial infarction, or stroke) may be ascribed to differences in achieved serum uric acid levels. Overall, serum uric acid may be a powerful tool to help stratify risk for cardiovascular disease. At the very least, it should be carefully considered when evaluating overall cardiovascular risk.

L4 ANSWER 27 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2004105282 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14996089
TITLE: Inhibitory influences of **xanthine oxidase inhibitor** and angiotensin I-converting enzyme inhibitor on multinucleated giant cell formation from monocytes by downregulation of adhesion molecules and purinergic receptors.
AUTHOR: Mizuno K; Okamoto H; Horio T

CORPORATE SOURCE: Department of Dermatology, Kansai Medical University, 10-15 Fumizono, Moriguchi, Osaka 570-8507, Japan.
SOURCE: British journal of dermatology, (2004 Feb) 150 (2) 205-10. Journal code: 0004041. ISSN: 0007-0963.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040304
Last Updated on STN: 20040430
Entered Medline: 20040429

AB BACKGROUND: Allopurinol, a **xanthine oxidase inhibitor**, and captopril, an inhibitor of angiotensin I-converting enzyme, are widely used for hyperuricaemia and **hypertension**, respectively. There have been reported cases showing that these two agents are effective for the treatment of granulomatous diseases such as sarcoidosis, although the mode of action is not elucidated. OBJECTIVES: We examined the in vitro effects of these agents on the formation of multinucleated giant cells (MGC) from human monocytes by concanavalin A-stimulated mononuclear cell supernatants (conditioned medium). METHODS: We cultured monocytes with conditioned medium and each agent and compared the rate of MGC formation as well as the expression of adhesion molecules and P2X7 receptor, which are involved in MGC formation. RESULTS: The addition of 25 or 100 microg mL(-1) allopurinol or 0.125-1.0 microg mL(-1) captopril inhibited MGC formation. Monocytes treated with these agents exhibited less expression of intercellular adhesion molecular-1 (ICAM-1) than untreated monocytes. The susceptibility of monocytes cultured in conditioned medium for 24 h to 2'-and 3'-o-(4-benzoyl-benzoyl)adenosine triphosphate-mediated cytolysis was significantly lower in monocytes treated with these agents than in untreated monocytes. CONCLUSIONS: Allopurinol and captopril have a therapeutic effect on granulomatous disorders by a direct action on monocyte/macrophage lineage cells partly through downregulation of ICAM-1 and P2X7 receptor.

L4 ANSWER 28 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003492340 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14499859
TITLE: Disproportionate enhancement of myocardial contractility by the xanthine oxidase inhibitor oxypurinol in failing rat myocardium.
COMMENT: Comment in: Cardiovasc Res. 2003 Sep 1;59(3):534-5. PubMed ID: 14499853
AUTHOR: Kogler Harald; Fraser Heather; McCune Sylvia; Altschuld Ruth; Marban Eduardo
CORPORATE SOURCE: Institute of Molecular Cardiobiology, Johns-Hopkins-University, Baltimore, MD, USA.. hkogler@med.uni-goettingen.de
CONTRACT NUMBER: R01 HL44065 (NHLBI)
R01 HL48835 (NHLBI)
SOURCE: Cardiovascular research, (2003 Sep 1) 59 (3) 582-92. Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031023
Last Updated on STN: 20040115
Entered Medline: 20040114

AB OBJECTIVE: Xanthine oxidase (XO) inhibitors enhance myofilament Ca(2+) responsiveness of normal rat myocardium. We examined whether this inotropic action is preserved or magnified in failing rat myocardium and whether the magnitude of this effect correlates with tissue xanthine-oxidoreductase (XOR) activity. METHODS: Hearts of 18-20

month-old SHHF (spontaneous hypertensive/heart failure) rats with end-stage heart failure, as well as of normal control rats, were perfused with the XO inhibitor oxypurinol. Afterwards, [Ca(2+)](i) and tension were measured simultaneously in fura-2-loaded intact isolated right ventricular trabeculae. XOR activity was determined fluorometrically in myocardial homogenates. RESULTS: In failing myocardium, 100 microM oxypurinol significantly increased systolic twitch tension (by 87 and 92% at 1.0 and 1.5 mM extracellular [Ca(2+)], respectively), without altering [Ca(2+)](i) transient amplitude. Oxypurinol did not alter the midpoint or cooperativity of the steady-state tension-[Ca(2+)](i) relationship, but significantly enhanced maximum Ca(2+)-activated tension by 75% in failing myocardium. Oxypurinol also exerted a positive inotropic effect in failing myocardium, which was, however, of significantly smaller relative magnitude. Failing rat myocardium exhibited higher XOR activity than nonfailing myocardium, and this activity was largely suppressed in oxypurinol-treated preparations. CONCLUSIONS: The magnitude of functional improvement with XOR inhibitors depends on the initial level of XOR activity. Specifically, the inotropic actions of oxypurinol are more pronounced in failing rat myocardium, a tissue that exhibits enhanced XOR activity. Our findings rationalize how XO inhibitors boost cardiac contractility and improve mechanoenergetic coupling, and why the effects might be relatively 'selective' for heart failure.

L4 ANSWER 29 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003089165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12600921
TITLE: Endothelin-1 increases vascular superoxide via endothelin(A)-NADPH oxidase pathway in low-renin **hypertension.**
AUTHOR: Li Lixin; Fink Gregory D; Watts Stephanie W; Northcott Carrie A; Galligan James J; Pagano Patrick J; Chen Alex F
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Michigan State University, East Lansing 48824-1317, USA.
SOURCE: Circulation, (2003 Feb 25) 107 (7) 1053-8.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030226
Last Updated on STN: 20030313
Entered Medline: 20030312

AB BACKGROUND: Angiotensin II-induced **hypertension** is associated with NAD(P)H oxidase-dependent superoxide production in the vessel wall. Vascular superoxide level is also increased in deoxycorticosterone acetate (DOCA)-salt **hypertension**, which is associated with a markedly depressed plasma renin activity because of sodium retention. However, the mechanisms underlying superoxide production in low-renin **hypertension** are undefined. METHODS AND RESULTS: This study investigated (1) whether and how endothelin-1 (ET-1), which is increased in DOCA-salt hypertensive rats, contributes to arterial superoxide generation and (2) the effect of gene transfer of manganese superoxide dismutase and endothelial nitric oxide synthase. Both superoxide and ET-1 levels were significantly elevated in carotid arteries of DOCA-salt rats compared with that of the sham-operated controls. ET-1 concentration-dependently stimulated superoxide production in vitro in carotid arteries of normotensive rats. The increase in arterial superoxide in both ET-1-treated normotensive and DOCA-salt rats was reversed by a selective ET(A) receptor antagonist, ABT-627, the flavoprotein inhibitor diphenyleneiodonium, and the NADPH oxidase inhibitor apocynin but not by the nitric oxide synthase inhibitor N(omega)-L-arginine methyl ester or the **xanthine oxidase inhibitor** allopurinol. Furthermore, in vivo blockade of ET(A) receptors significantly reduced arterial superoxide levels, with a

concomitant decrease of systolic blood pressure in DOCA-salt rats. Ex vivo gene transfer of manganese superoxide dismutase or endothelial nitric oxide synthase also suppressed superoxide levels in carotid arteries of DOCA-salt rats. CONCLUSIONS: These findings suggest that ET-1 augments vascular superoxide production at least in part via an ET(A)/NADPH oxidase pathway in low-renin mineralocorticoid **hypertension.**

L4 ANSWER 39 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002682785 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12444207
TITLE: A role for uric acid in the progression of renal disease.
AUTHOR: Kang Duk-Hee; Nakagawa Takahiko; Feng Lili; Watanabe Susumu; Han Lin; Mazzali Marilda; Truong Luan; Harris Raymond; Johnson Richard J
CORPORATE SOURCE: Division of Nephrology, Baylor College of Medicine, Houston, Texas, USA.. dhkang@ewha.ac.kr
CONTRACT NUMBER: HL 68607 (NHLBI)
R01 DK 52121 (NIDDK)
SOURCE: Journal of the American Society of Nephrology : JASN, (2002 Dec) 13 (12) 2888-97.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20021122
Last Updated on STN: 20030508
Entered Medline: 20030507

AB Hyperuricemia is associated with renal disease, but it is usually considered a marker of renal dysfunction rather than a risk factor for progression. Recent studies have reported that mild hyperuricemia in normal rats induced by the uricase inhibitor, oxonic acid (OA), results in **hypertension**, intrarenal vascular disease, and renal injury. This led to the hypothesis that uric acid may contribute to progressive renal disease. To examine the effect of hyperuricemia on renal disease progression, rats were fed 2% OA for 6 wk after 5/6 remnant kidney (RK) surgery with or without the **xanthine oxidase** inhibitor, allopurinol, or the uricosuric agent, benziodarone. Renal function and histologic studies were performed at 6 wk. Given observations that uric acid induces vascular disease, the effect of uric acid on vascular smooth muscle cells in culture was also examined. RK rats developed transient hyperuricemia (2.7 mg/dl at week 2), but then levels returned to baseline by week 6 (1.4 mg/dl). In contrast, RK+OA rats developed higher and more persistent hyperuricemia (6 wk, 3.2 mg/dl). Hyperuricemic rats demonstrated higher BP, greater proteinuria, and higher serum creatinine than RK rats. Hyperuricemic RK rats had more renal hypertrophy and greater glomerulosclerosis (24.2 +/- 2.5 versus 17.5 +/- 3.4%; $P < 0.05$) and interstitial fibrosis (1.89 +/- 0.45 versus 1.52 +/- 0.47; $P < 0.05$). Hyperuricemic rats developed vascular disease consisting of thickening of the preglomerular arteries with smooth muscle cell proliferation; these changes were significantly more severe than a historical RK group with similar BP. Allopurinol significantly reduced uric acid levels and blocked the renal functional and histologic changes. Benziodarone reduced uric acid levels less effectively and only partially improved BP and renal function, with minimal effect on the vascular changes. To better understand the mechanism for the vascular disease, the expression of COX-2 and renin were examined. Hyperuricemic rats showed increased renal renin and COX-2 expression, the latter especially in preglomerular arterial vessels. In in vitro studies, cultured vascular smooth muscle cells incubated with uric acid also generated COX-2 with time-dependent proliferation, which was prevented by either a COX-2 or TXA-2 receptor inhibitor. Hyperuricemia accelerates renal progression in the RK model via a mechanism linked to high systemic BP and COX-2-mediated, thromboxane-induced vascular disease. These studies

provide direct evidence that uric acid may be a true mediator of renal disease and progression.

L4 ANSWER 31 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2001665732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11711506
TITLE: NADH/NADPH oxidase and enhanced superoxide production in the mineralocorticoid hypertensive rat.
AUTHOR: Beswick R A; Dorrance A M; Leite R; Webb R C
CORPORATE SOURCE: Department of Physiology, Medical College of Georgia, Augusta, USA.. rbeswick@umich.edu
CONTRACT NUMBER: 2-T32-GME0322-11 (NIGMS)
HL-18575 (NHLBI)
SOURCE: Hypertension, (2001 Nov) 38 (5) 1107-11.
Journal code: 7906255. ISSN: 1524-4563.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011119
Last Updated on STN: 20020123
Entered Medline: 20011207

AB We previously reported increased aortic reactive oxygen species (ROS) production in mineralocorticoid (deoxycorticosterone acetate [DOCA]-salt) hypertensive rats. In the present study, we tested the hypothesis that NADH/NADPH oxidase is responsible for increased ROS production, namely superoxide (O(2-)), in aorta from the DOCA-salt rat. Treatment of aortic rings from DOCA-salt rats with the NO synthase inhibitor N-nitro-L-arginine and the **xanthine oxidase inhibitor** allopurinol did not significantly change O(2-) production. Furthermore, de-endothelialization of aorta from DOCA-salt rats did not affect O(2-) production compared with that of sham-operated rats. Thus, xanthine oxidase and uncoupled endothelial NO synthase were not responsible for increased O(2-) production in the DOCA-salt rats. In contrast, treatment with the NADPH oxidase inhibitor apocynin significantly decreased O(2-) production in aortic rings from DOCA-salt rats compared with sham-operated rats. Moreover, long-term administration of apocynin (in drinking water, 1.5 mmol/L, 28 days) to DOCA-salt rats significantly decreased systolic blood pressure compared with that of rats treated with DOCA-salt alone. Furthermore, O(2-) production in aortic rings from DOCA-salt rats treated with apocynin for 28 days was reduced compared with that of untreated DOCA-salt rats. Reverse transcriptase-polymerase chain reaction (RT-PCR) analysis demonstrated that DOCA-salt rats have significantly greater mRNA levels of the NADPH oxidase subunit p22phox than do sham-operated rats. These findings suggest that NADPH oxidase is increased and is responsible for increased O(2-) production and possibly contributes to increased blood pressure in the DOCA-salt hypertensive rat.

L4 ANSWER 32 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2001665731 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11711505
TITLE: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism.
AUTHOR: Mazzali M; Hughes J; Kim Y G; Jefferson J A; Kang D H; Gordon K L; Lan H Y; Kivlighn S; Johnson R J
CORPORATE SOURCE: Division of Nephrology, University of Washington Medical Center, Seattle, USA.. m_mazzali@hotmail.com
CONTRACT NUMBER: DK-47659 (NIDDK)
SOURCE: Hypertension, (2001 Nov) 38 (5) 1101-6.
Journal code: 7906255. ISSN: 1524-4563.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011119
Last Updated on STN: 20020123
Entered Medline: 20011207

AB An elevation in circulating serum uric acid is strongly associated with the development of hypertension and renal disease, but whether uric acid has a causal role or whether it simply indicates patients at risk for these complications remains controversial. We tested the hypothesis that uric acid may have a causal role in the development of **hypertension** and renal disease by examining the effects of mild hyperuricemia in rats. Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 weeks, whereas control rats remained normotensive. The development of **hypertension** was prevented by concurrent treatment with either a **xanthine oxidase inhibitor** (allopurinol) or a uricosuric agent (benziodarone), both of which lowered uric acid levels. Blood pressure could also be lowered by reducing uric acid levels with either allopurinol or oxonic acid withdrawal. A direct relationship was found between blood pressure and uric acid ($r=0.75$, $n=69$), with a 10-mm Hg blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid. The kidneys were devoid of urate crystals and were normal by light microscopy. However, immunohistochemical stains documented an ischemic type of injury with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin. Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal NO synthase. Both the renal injury and **hypertension** were reduced by treatment with enalapril or L-arginine. In conclusion, mild hyperuricemia causes **hypertension** and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.

L4 ANSWER 33 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2000187418 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10720589
TITLE: Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension.
AUTHOR: Butler R; Morris A D; Belch J J; Hill A; Struthers A D
CORPORATE SOURCE: University Department of Clinical Pharmacology and Therapeutics, University Department of Medicine, and The Diabetes Centre, Ninewells Hospital and Medical School, Dundee, UK.
SOURCE: Hypertension, (2000 Mar) 35 (3) 746-51.
Journal code: 7906255. ISSN: 1524-4563.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20010521
Entered Medline: 20000403

AB Therapeutic strategies against free radicals have mostly focused on the augmentation of antioxidant defenses (eg, vitamins C and E). A novel approach is to prevent free radical generation by the enzyme system xanthine oxidase. We examined whether the inhibition of xanthine oxidase with allopurinol can improve endothelial function in subjects with type 2 diabetes and coexisting mild **hypertension** compared with control subjects of a similar age. We examined 23 subjects (11 patients with type 2 diabetes and 12 healthy age-matched control subjects) in 2 parallel groups. The subjects were administered 300 mg allopurinol in a

randomized, placebo-controlled study in which both therapies were administered for 1 month. Endothelial function was assessed with bilateral venous occlusion plethysmography, in which the forearm blood flow responses to intra-arterial infusions of endothelium-dependent and -independent vasodilators were measured. Allopurinol significantly increased the mean forearm blood flow response to acetylcholine by 30% (3.16+/-1.21 versus 2.34+/-0.76 mL. 100 mL(-1). min(-1) allopurinol versus placebo; P=0.012, 95% CI 0.14, 1.20) but did not affect the nitroprusside response in patients with type 2 diabetes. There was no significant impact on either endothelium-dependent or -independent vascular responses in age-matched control subjects. Allopurinol improved endothelial function to near-normal levels. Regarding markers of free radical activity, the level of malondialdehyde was significantly reduced (0.30+/-0.04 versus 0. 34+/-0.05 micromol/L for allopurinol versus placebo, P=0.03) in patients with type 2 diabetes but not in control subjects. The **xanthine oxidase inhibitor** allopurinol improves endothelial dysfunction in patients with type 2 diabetes with mild **hypertension** but not in matched control subjects. In the former group, allopurinol restored endothelial function to near-normal levels.

L4 ANSWER 34 OF 40 MEDLINE on STN
ACCESSION NUMBER: 1998275247 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9612300
TITLE: Nitric oxide exposure inhibits endothelial NOS activity but not gene expression: a role for superoxide.
AUTHOR: Sheehy A M; Burson M A; Black S M
CORPORATE SOURCE: Department of Pediatrics, University of California, San Francisco 94143-0106, USA.
SOURCE: American journal of physiology, (1998 May) 274 (5 Pt 1) L833-41.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980701

AB Recent studies have characterized a rebound pulmonary vasoconstriction with abrupt withdrawal of inhaled nitric oxide (NO) during therapy for pulmonary **hypertension**, suggesting that inhaled NO may downregulate basal NO production. However, the exact mechanism of this rebound pulmonary **hypertension** remains unclear. The objectives of these studies were to determine the effect of NO exposure on endothelial NO synthase (eNOS) gene expression, enzyme activity, and posttranslational modification in cultured pulmonary arterial endothelial cells. Sodium nitroprusside (SNP) treatment had no effect on eNOS mRNA or protein levels but did produce a significant decrease in enzyme activity. Furthermore, although SNP treatment induced protein kinase C (PKC)-dependent eNOS phosphorylation, blockade of PKC activity did not protect against the effects of SNP. When the **xanthine oxidase inhibitor** allopurinol or the superoxide scavenger 4,5-dihydroxy-1-benzene-disulfonic acid were co-incubated with SNP, the inhibitory effects on eNOS activity could be partially alleviated. Also, the levels of superoxide were found to be elevated 4.5-fold when cultured pulmonary arterial endothelial cells were exposed to the NO donor spermine/NO. This suggests that NO can stimulate xanthine oxidase to cause an increase in cellular superoxide generation. A reaction between NO and superoxide would produce peroxynitrite, which could then react with the eNOS protein, resulting in enzyme inactivation. This mechanism may explain, at least in part, how NO produces NOS inhibition in vivo and may delineate, in part, the mechanism of rebound pulmonary **hypertension** after withdrawal of inhaled NO.

L4 ANSWER 35 OF 40 MEDLINE on STN
ACCESSION NUMBER: 97375504 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9231821
TITLE: Xanthine oxidase inhibition with oxypurinol improves endothelial vasodilator function in hypercholesterolemic but not in hypertensive patients.
AUTHOR: Cardillo C; Kilcoyne C M; Cannon R O 3rd; Quyyumi A A; Panza J A
CORPORATE SOURCE: Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md 20892-1650, USA.
SOURCE: Hypertension, (1997 Jul) 30 (1 Pt 1) 57-63.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970825
Last Updated on STN: 19970825
Entered Medline: 19970808

AB Hypercholesterolemic and hypertensive patients have impaired endothelium-dependent vasorelaxation because of decreased nitric oxide activity, but the mechanism underlying this abnormality is unknown. This study sought to determine whether an increased breakdown of nitric oxide by xanthine oxidase-generated superoxide anions could participate in these forms of endothelial dysfunction. We studied vascular responses to intrabrachial infusion of acetylcholine (an endothelium-dependent vasodilator, 7.5 to 30 microg/min) and sodium nitroprusside (a direct smooth muscle dilator, 0.8 to 3.2 microg/min) by strain-gauge plethysmography before and during the combined administration of oxypurinol (300 microg/min), a **xanthine oxidase inhibitor**, in 20 hypercholesterolemic patients, 20 essential hypertensive patients, and 20 normal subjects. The vasodilator response to acetylcholine was blunted in hypercholesterolemic (highest flow, 8.2+/-8 mL x min(-1) x dL(-1)) and hypertensive (8.5+/-4 mL x min(-1) x dL(-1)) patients compared with control subjects (13.8+/- 6.6 mL x min(-1) x dL(-1)) (both P<.001); however, no differences were observed in the response to sodium nitroprusside. Oxypurinol did not change the response to acetylcholine in control subjects (P=.26) and improved, but did not normalize, its vasodilator effect in hypercholesterolemic patients (P<.01). Oxypurinol did not affect the response to acetylcholine in hypertensive patients (P=.34) and did not modify the response to sodium nitroprusside in any group. These results suggest that xanthine oxidase-generated superoxide anions are partly responsible for the impaired endothelial vasodilator function of hypercholesterolemic patients. In contrast, this mechanism does not appear to play a significant role in essential **hypertension.**

L4 ANSWER 36 OF 40 MEDLINE on STN
ACCESSION NUMBER: 96189209 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8618943
TITLE: Potentiation of nitric oxide-mediated vasorelaxation by **xanthine oxidase inhibitors.**
AUTHOR: Miyamoto Y; Akaike T; Yoshida M; Goto S; Horie H; Maeda H
CORPORATE SOURCE: Department of Microbiology, Kumamoto University School of Medicine, Japan.
SOURCE: Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N. Y.), (1996 Apr) 211 (4) 366-73.
Journal code: 7505892. ISSN: 0037-9727.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960620
Last Updated on STN: 19960620
Entered Medline: 19960612

AB Nitric oxide (NO), now almost synonymous with endothelium-derived relaxing factor (EDRF), reacts with superoxide anion radical (O2-) and forms a potentially toxic molecular species, peroxynitrite (ONOO-). Because xanthine oxidase (XO) seems to be a major O2- -producing enzyme in the vascular system, it is important to clarify the mechanism of XO regulation of NO/EDRF. We first characterized the inhibition of XO in vitro by three types of pyrazolopyrimidine derivatives. Kinetic studies indicated that 4-amino-6-hydroxpyrazolo[3,4-d]pyrimidine (AHPP) and allopurinol competitively inhibited the conversion of xanthine to uric acid catalyzed by XO, with apparent Ki values of 0.17 +/- 0.02 and 0.50 +/- 0.03 micro M respectively; alloxanthine inhibited this conversion in a noncompetitive manner with an apparent Ki value of 3.54 +/- 1.12 microM. O2- generation in the xanthine/XO system assayed by lucigenin-dependent chemiluminescence was suppressed most strongly by AHPP in a dose-dependent fashion; allopurinol itself appears to reduce the enzyme by transfer of an electron to O2, thus generating O(2-). AHPP significantly augmented EDRF-mediated relaxation of aortic rings from both rabbits and spontaneously hypertensive rats (SHR) in a dose-dependent manner, whereas allopurinol did not affect the relaxation and only marginal potentiation of the vasorelaxation was observed with alloxanthine. Finally, iv injection of AHPP (50.4 mg/kg; 100 micromol/300 g rat) reduced the blood pressure of SHR rats to 70% of the initial pressure; this pressure is almost the blood pressure of normal rats. Allopurinol (100 micromol/300 g rat; iv) showed transient decrease in blood pressure and moderate reduction of **hypertension** of SHR (10%) was observed with iv injection of alloxanthine (100 mumol/300 g rat). On the basis of these results, it seems that XO regulates EDRF/NO via production of O2-.

L4 ANSWER 37 OF 40 MEDLINE on STN
ACCESSION NUMBER: 95255903 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7737720
TITLE: In vivo evidence for microvascular oxidative stress in spontaneously hypertensive rats. Hydroethidine microfluorography.
AUTHOR: Suzuki H; Swei A; Zweifach B W; Schmid-Schonbein G W
CORPORATE SOURCE: Institute for Biomedical Engineering, University of California at San Diego, La Jolla 92093-0412, USA.
CONTRACT NUMBER: HL-10881 (NHLBI)
SOURCE: Hypertension, (1995 May) 25 (5) 1083-9.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950615
Last Updated on STN: 19950615
Entered Medline: 19950606

AB The factors that predispose to the accelerated organ injury that accompanies the hypertensive syndrome have remained speculative and without a firm experimental basis. Indirect evidence has suggested that a key feature may be related to an enhanced oxygen radical production. The purpose of this study was to refine and use a technique to visualize evidence of spontaneous microvascular oxidative stress in vivo in the spontaneously hypertensive rat (SHR) compared with its normotensive control, the Wistar-Kyoto rat (WKY). We investigated the effects of adrenal glucocorticoids on the microvascular oxidative stress sequence. The mesentery was superfused with hydroethidine, a reduced, nonfluorescent precursor of ethidium bromide. In the presence of oxidative challenge, hydroethidine is transformed intracellularly into the fluorescent compound

ethidium bromide, which binds to DNA and can be detected by virtue of its red fluorescence. The fluorescent light emission from freshly exteriorized and otherwise unstimulated mesentery microvessels was recorded by digital microscopy. The number of ethidium bromide-positive nuclei along the arteriolar and venular walls in SHR was found to be significantly increased above the level exhibited by WKY. The elevation in ethidium bromide fluorescence in SHR arterioles could be attenuated by a synthetic glucocorticoid inhibitor and in rats subjected to adrenalectomy. The administration of glucocorticoids after adrenalectomy by injection of dexamethasone restored the oxidative reaction in SHR arterioles. Treatment with dimethylthiourea and with a **xanthine oxidase inhibitor** attenuated the superoxide formation. Although a nitric oxide synthase inhibitor (NG-nitro-L-arginine methyl ester) enhanced the ethidium bromide staining in WKY, it did not affect that in SHR.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 38 OF 40 MEDLINE on STN
ACCESSION NUMBER: 95174946 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7870233
TITLE: Allopurinol fails to protect against gentamicin-induced renal damage in normotensive and spontaneously hypertensive rats.
AUTHOR: Smyth B J; Davis W G
CORPORATE SOURCE: Department of Pathology, Medical University of South Carolina, Charleston 29425-2645.
SOURCE: Nephron, (1994) 68 (4) 468-72.
Journal code: 0331777. ISSN: 0028-2766.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950407
Last Updated on STN: 19950407
Entered Medline: 19950330

AB Recent research suggests the involvement of hydroxyl and superoxide free radicals in the development of gentamicin-induced acute renal tubular necrosis. Xanthine oxidase has been implicated as an important source of superoxide free radicals. Spontaneously hypertensive (Wistar-Kyoto) rats (SHR) have excessive oxidant stress which may render them more sensitive to the proported oxygen free radical producing effects of gentamicin. This study was undertaken to determine if the **xanthine oxidase inhibitor** allopurinol will ameliorate the effects of gentamicin. Normotensive Wistar-Kyoto (WKY) rats and SHR were administered allopurinol (40 mg/kg twice daily) orally 4 days before and throughout a 12-day gentamicin treatment period. The allopurinol only treatment group demonstrated no noticeable histological or functional changes considered to be indicative of nephrotoxicity. Gentamicin-injected WKY rats and SHR equally demonstrated extensive proximal tubular and glomerular damage characteristic of aminoglycoside-induced kidney damage. Allopurinol failed to protect either rat strain against the histological damage caused by gentamicin. Equivalent alterations in serum creatinine, serum gentamicin, urinary N-acetyl-beta-D-glucosaminidase excretion, body weight, urinary output, and blood pressure occurred in the gentamicin with allopurinol and gentamicin only treatment groups. Our results demonstrate allopurinol does not ameliorate the pathogenesis of gentamicin. SHR do not appear to be more sensitive to the effects of gentamicin induced kidney damage with or without allopurinol as compared with WKY rats.

L4 ANSWER 39 OF 40 MEDLINE on STN
ACCESSION NUMBER: 93212350 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8460415
TITLE: Protective effects of therapy with a protease and **xanthine oxidase inhibitor** in

short form pancreatic biliary obstruction and ischemia in rats.
AUTHOR: Hirano T; Manabe T; Steer M; Printz H; Calne R; Tobe T
CORPORATE SOURCE: Department of Surgery, Addenbrookes Hospital, Cambridge, England.
SOURCE: Surgery, gynecology & obstetrics, (1993 Apr) 176 (4) 371-81.
Journal code: 0101370. ISSN: 0039-6087.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19930514
Entered Medline: 19930428

AB The current study was done to evaluate the effects of short term (60 minutes) pancreatic biliary duct obstruction (PBDO) with intraductal **hypertension** (IDH) stimulated by secretin (0.2 clinical unit per kilogram per hour) and caerulein (0.2 microgram per kilogram per hour) plus 30 minutes of temporary pancreatic ischemia (ISCH) produced by ligation of celiac and superior mesenteric artery on the exocrine pancreas and protective effects of a new potent protease inhibitor, ONO3307 in combination with **xanthine oxidase inhibitor**, allopurinol, in this multifactor related model of acute pancreatitis in rats. Twelve hours after PBDO with IDH plus ISCH, we observed hyperamylasemia (23 +/- 3 units per milliliter) ($p < 0.01$); moderate pancreatic histologic changes; pancreatic edema (water content--81 +/- 2 percent) ($p < 0.02$), as well as the impaired amylase (2,889 +/- 328 units per kilogram per hour) ($p < 0.01$) and cathepsin B output (7 +/- 3 units per kilogram per hour) ($p < 0.01$) into the pancreatic juice of rats stimulated by caerulein (control group--serum amylase levels, 6 +/- 1 units per milliliter; pancreatic water content, 74 +/- 1 percent. Furthermore, PBDO with IDH plus ISCH caused the redistribution of lysosomal enzyme from lysosomal fraction (12 kilo times gravity pellet; 40 +/- 3 percent; $p < 0.01$) to zymogen fraction (1.3 kilo times gravity pellet; 38 +/- 3 percent; $p < 0.01$) (control group--12 kilo times gravity pellet, 59 +/- 2 percent; 1.3 kilo times gravity pellet, 24 +/- 2 percent) and the impaired pancreatic adenylate energy metabolism (0.79 +/- 0.02, $p < 0.02$) (control group--energy charge equals 0.88 +/- 0.01). Only PBDO with IDH caused no significant changes. Although only ONO3307 or allopurinol therapy showed the partial significant protective effects against pancreatic injuries, improving serum amylase levels, the administration of ONO3307 in combination therapy with allopurinol showed almost complete protective effects against the pancreatic injuries induced by PBDO with IDH plus ISCH (serum amylase levels, 9 +/- 2 units per milliliter; pancreatic water content, 76 +/- 2 percent; amylase and cathepsin B output, 7,127 +/- 946 and 18 +/- 3 units per kilogram per hour; 1.3 kilo times gravity pellet, 28 +/- 2 percent; 12 kilo times gravity pellet, 54 +/- 2 percent, and energy charge equals 0.85 +/- 0.02).(ABSTRACT TRUNCATED AT 400 WORDS)

L4 ANSWER 40 OF 40 MEDLINE on STN
ACCESSION NUMBER: 93209170 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7681372
TITLE: Prevention and management of gout.
AUTHOR: Star V L; Hochberg M C
CORPORATE SOURCE: Department of Medicine, University of Maryland School of Medicine, Baltimore.
SOURCE: Drugs, (1993 Feb) 45 (2) 212-22. Ref: 35
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19960129
Entered Medline: 19930429

AB Gout is a common disease with a worldwide distribution. The major risk factor for the development of gout is sustained asymptomatic hyperuricaemia. Although pharmacological therapy of asymptomatic hyperuricaemia is not recommended, primary prevention of gout can be achieved through lifestyle changes including weight loss, restricting protein and calorie intake, limiting alcohol consumption, avoiding the use of diuretics in the treatment of **hypertension**, and avoiding occupational exposure to lead. The arthritis of gout can be readily managed with the use of nonsteroidal anti-inflammatory drugs (NSAIDs); systemic steroids or corticotrophin (adrenocorticotrophic hormone; ACTH) should be used in patients with contraindications to NSAIDs, or who are intolerant of them. Because of potential toxicity, colchicine should not be used to treat acute gout, but should be used in low dosage (0.6 to 1.2 mg/day) for prophylaxis of recurrent attacks of gout. The other cornerstone of prevention of recurrent gouty attacks is control of hyperuricaemia, which can be effectively accomplished with antihyperuricaemic therapy. The choice of agents, either uricosuric drugs or **xanthine oxidase inhibitors**, is based on the level of urinary uric acid excretion, renal function, age of patient, history of renal calculi and presence of tophi. Treatment and prevention of gout are exceedingly effective and patients can usually be managed by their primary care physician.

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=>
=> s xanthine oxidase and inhibition
L5        3548 XANTHINE OXIDASE AND INHIBITION

=> d hist

     (FILE 'HOME' ENTERED AT 13:28:28 ON 01 APR 2005)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 13:28:43 ON 01 APR 2005
L1          1214 S XANTHINE OXIDASE INHIBITOR?
L2          1166 S XANTHINE OXIDASE INHIBITOR
L3        306913 S HYPERTENSION
L4            40 S L1 AND L3
L5          3548 S XANTHINE OXIDASE AND INHIBITION

=> s L4 and L4
L6            40 L4 AND L4

=> s uric acid?
L7        38472 URIC ACID?

=> s L3 and L7
L8         2565 L3 AND L7

=> s uric acid lowering agent
L9           11 URIC ACID LOWERING AGENT

=> d 1-11 L9 ibib abs

L9   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:          2002:10270  CAPLUS
DOCUMENT NUMBER:           136:64126
TITLE:                     Agent reducing uric acid levels for treatment of
                           cardiovascular disease and hypertension
INVENTOR(S):               Kivlighn, Salah; Johnson, Richard J.; Mazzali, Marilda
PATENT ASSIGNEE(S):        Merck & Co., Inc., USA; University of Washington
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SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000210	A2	20020103	WO 2001-US20457	20010628
WO 2002000210	A3	20021024		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2413201	AA	20020103	CA 2001-2413201	20010628
US 2002019360	A1	20020214	US 2001-892505	20010628
EP 1317258	A2	20030611	EP 2001-946722	20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517804	T2	20040617	JP 2002-504992	20010628

PRIORITY APPLN. INFO.: US 2000-214825P P 20000628
WO 2001-US20457 W 20010628

AB This invention relates to a method for treating and preventing hypertension by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Addnl., the scope of the invention includes a method of treating coronary heart disease by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Allopurinol administered from the initiation of an oxonic acid diet prevented the development of hyperuricemia and hypertension. In hypertensive, hyperuricemic rats, either withdrawal of the oxonic acid or adding allopurinol also resulted in a reduction in the blood pressure in association with a fall in serum uric acid values.

L9 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:379871 CAPLUS
DOCUMENT NUMBER: 135:147004
TITLE: A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis
AUTHOR(S): Goldman, Stanton C.; Holcenberg, John S.; Finklestein, Jerry Z.; Hutchinson, Raymond; Kreissman, Susan; Johnson, F. Leonard; Tou, Conrad; Harvey, Elizabeth; Morris, Erin; Cairo, Mitchell S.
CORPORATE SOURCE: Department of Pediatric Hematology/Oncology, North Texas Hospital for Children at Medical City, Dallas, TX, USA
SOURCE: Blood (2001), 97(10), 2998-3003
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Standard therapy in the United States for malignancy-associated hyperuricemia consists of hydration, alkalinization, and allopurinol. Urate oxidase catalyzes the enzymic oxidation of uric acid to a 5 times increased urine soluble product, allantoin. Rasburicase is a new recombinant form of urate oxidase available for clin. evaluation. This multicenter randomized trial

compared allopurinol to rasburicase in pediatric patients with leukemia or lymphoma at high risk for tumor lysis. Patients received the assigned **uric acid-lowering agent** for 5 to 7 days during induction chemotherapy. The primary efficacy end point was to compare the area under the serial plasma uric acid concentration curves during the first 96 h of therapy (AUC0-96). Fifty-two patients were randomized at 6 sites. In an intent-to-treat anal., the mean uric acid AUC0-96 was 128 ± 70 mg/dL.hour for the rasburicase group and 329 ± 129 mg/dL.hour for the allopurinol group (P < .0001). The rasburicase vs. allopurinol group experienced a 2.6-fold (95% CI: 2.0-3.4) less exposure to uric acid. Four hours after the first dose, patients randomized to rasburicase compared to allopurinol achieved an 86% vs. 12% reduction (P < .0001) of initial plasma uric acid levels. No antirasburicase antibodies were detected at day 14. This randomized study demonstrated more rapid control and lower levels of plasma uric acid in patients at high risk for tumor lysis who received rasburicase compared to allopurinol. For pediatric patients with advanced stage lymphoma or high tumor burden leukemia, rasburicase is a safe and effective alternative to allopurinol during initial chemotherapy.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:569285 CAPLUS

DOCUMENT NUMBER: 129:301145

TITLE: Decreased serum concentrations of 1,25(OH)2-vitamin D3 in patients with gout

AUTHOR(S): Takahashi, Sumio; Yamamoto, Tetsuya; Moriwaki, Yuji; Tsutsumi, Zenta; Yamakita, Jun-ichi; Higashino, Kazuya

CORPORATE SOURCE: Third Department Internal Medicine, Hyogo College Medicine, Nishinomiya, Hyogo, 663, Japan

SOURCE: Advances in Experimental Medicine and Biology (1998), 431(Purine and Pyrimidine Metabolism in Man IX, 1998), 57-60
CODEN: AEMBAP; ISSN: 0065-2598

PUBLISHER: Plenum Publishing Corp.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors measured the serum concns. of 1,25(OH)2-vitamin D3, 25(OH)-vitamin D3, parathyroid hormone (PTH) in 82 male patients with primary gout whose serum uric acid was significantly higher than that of 41 normal control male subjects (8.8 vs. 5.6 mg/dL). The serum 1,25(OH)2-vitamin D3 concentration was significantly lower in the patients with gout compared with the control subjects (39.6 vs. 44.8 pg/mL), while no differences were observed between the two groups in either the serum concentration of 25(OH)-vitamin D3 or PTH. The administration of **uric acid lowering agent** to the patients for 1 yr caused a significant increase in their serum 1,25(OH)2-vitamin D3 concentration which was associated with a significant decrease in their serum uric acid concentration In contrast, the serum concns. of 25(OH)-vitamin D3 and PTH were not affected by these drugs. These results suggest that uric acid per se may directly decrease the serum concentration of 1,25(OH)2-vitamin D3 in patients with gout by inhibiting 1-hydroxylase activity.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1992:221600 CAPLUS

DOCUMENT NUMBER: 116:221600

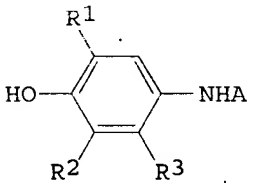
TITLE: Serum **uric acid-lowering agents** containing 4-(heteroarylamino)phenols

INVENTOR(S): Shibata, Hisao; Kubo, Hideji; Matsuno, Taro; Kamisako, Takuji

PATENT ASSIGNEE(S): Otsuka Pharmaceutical Factory, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 04018021	A2	19920122	JP 1990-301610	19901106
PRIORITY APPLN. INFO.:			JP 1989-292894	A1 19891109

OTHER SOURCE(S): MARPAT 116:221600
GI



I

AB Serum **uric acid-lowering agents** containing aminophenols I [R1 = lower alkyl; R2, R3 = H, lower alkyl; R2R3 may be (CH2)4, (CH:CH)2; A = N, O, or S-containing 5- or 6-membered heterocyclyl, pyrazine-N-oxide group, pyridazine-N-oxide group, pyrimidine-N-oxide group, which may be substituted with lower alkyl, halo, Ph, lower alkoxycarbonyl, NH2, lower alkoxy, lower hydroxyalkyl] and/or their salts as active ingredient(s) are claimed. A composition containing I (R1 = R2 = CMe3, R3 = H, A = pyrazinyl) 100, Avicel PH 101 40, corn starch 30, and Mg stearate 2 g was made into sugar-coated tablets, which were coated with a composition containing TC-5 (hydroxypropyl Me cellulose) 8, polyethylene glycol 6000 2.4, colorant 0.6, TiO2 4.0, and H2O 85.0 g to give 1000 film-coating tablets. The tablets were administered to healthy volunteers at 2 tablets/day for 8 days to show significant serum uric acid-lowering activity.

L9 ANSWER 5 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2004492967 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15461235
TITLE: Crystal arthritis. Gout and pseudogout in the geriatric patient.
AUTHOR: Cassetta Michael; Gorevic Peter D
CORPORATE SOURCE: Mount Sinai Medical Center, New York, NY, USA.
SOURCE: Geriatrics, (2004 Sep) 59 (9) 25-30; quiz 31. Ref: 24.
Journal code: 2985102R. ISSN: 0016-867X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20041006
Last Updated on STN: 20041015
Entered Medline: 20041014

AB Gout and pseudogout are inflammatory arthritides due to monosodium urate and calcium pyrophosphate dihydrate crystal formation. Both are prevalent

among geriatric patients, and can present as acute mono- or oligoarticular disease, or as a chronic polyarthropathy resembling osteoarthritis or rheumatoid arthritis. Gout in the geriatric patient is a disease affecting women, commonly associated with diuretic usage, often involves the fingers, may be complicated by the development of masses of uric acid crystals (tophi) in soft tissues, and is frequently polyarticular. Pseudogout in the geriatric patient has a variety of clinical presentations, may be acute or chronic, and should be considered in evaluating any patient with osteoarthritis occurring in an atypical distribution. Treatment includes the use of nonsteroidal anti-inflammatory drugs, colchicine, or corticosteroids. Gout may be impacted by dietary factors, weight reduction, and avoidance of certain forms of alcohol; **uric acid-lowering agents** are effective for refractory or chronic tophaceous disease.

L9 ANSWER 6 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2004396008 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15299172
TITLE: Gout: a review of its aetiology and treatment.
COMMENT: Comment in: Hong Kong Med J. 2004 Oct;10(5):367. PubMed ID: 15479974
AUTHOR: Li E K
CORPORATE SOURCE: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong.. edmundli@cuhk.edu.hk
SOURCE: Hong Kong medical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine, (2004 Aug) 10 (4) 261-70. Ref: 66
Journal code: 9512509. ISSN: 1024-2708.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200412
ENTRY DATE: Entered STN: 20040810
Last Updated on STN: 20041223
Entered Medline: 20041222

AB OBJECTIVE: To review the current understanding of the causes and the management of gout. DATA SOURCES: Publications on all peer-review literature from MEDLINE from 1965 to January 2004. STUDY SELECTION: Selected and evaluated by the author. DATA EXTRACTION: Extracted and evaluated by the author. DATA SYNTHESIS: The underlying metabolic disorder in gout is hyperuricaemia. Most patients with hyperuricaemia remain asymptomatic throughout their lifetime. The phase of asymptomatic hyperuricaemia ends with the first attack of gouty arthritis or urolithiasis. The risk of gout and stone formation is increased with the degree and duration of hyperuricaemia. Drugs available for the treatment of acute gouty arthritis, such as non-steroidal anti-inflammatory drugs, selective cyclo-oxygenase 2 inhibitors, systemic corticosteroids, or colchicine, are effective. For periods between attacks, prophylactic therapy, such as low-dose colchicine, is effective. In those with recurrent attacks of more than two to three times yearly, a **uric acid-lowering agent** as a long-term therapy should be considered to avoid recurrence and the development of tophaceous gout. CONCLUSIONS: Effective management of gout can be achieved through better understanding of the causes of the condition, preventive measures as well as drug treatment.

L9 ANSWER 7 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2003001790 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12508389
TITLE: Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout.

COMMENT: Erratum in: J Rheumatol. 2003 Feb;30(2):423
AUTHOR: de Klerk Erik; van der Heijde Desiree; Landewe Robert; van der Tempel Hille; Urquhart John; van der Linden Sjef
CORPORATE SOURCE: Division of Rheumatology, University Hospital Maastricht, The Netherlands.
SOURCE: Journal of rheumatology, (2003 Jan) 30 (1) 44-54.
Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030102
Last Updated on STN: 20030514
Entered Medline: 20030513

AB OBJECTIVE: (1) To explore patient compliance with prescribed drug regimens in the setting of usual care for outpatients with rheumatoid arthritis (RA), gout, and polymyalgia rheumatica (PMR) by utilizing electronic medication event monitors (MEMS(R)) to register openings of the medication package. (2) To examine the influence of disease, frequency of intake of the drug, and class of drug on compliance. (3) To explore the influence of demographic factors, quality of life measures, coping, health status, and functional ability as potential predictors of patient compliance.
METHODS: A total of 127 consenting consecutive patients were enrolled: 81 patients with RA, 33 taking nonsteroidal antiinflammatory drugs (13 diclofenac TID and 20 naproxen BID) and 48 taking disease modifying antirheumatic drugs [25 sulfasalazine (SSZ) BID and 23 methotrexate (MTX) once weekly]; 17 patients with PMR starting with prednisolone QD; and 29 patients with gout starting with colchicine (12, QD) or starting with **uric acid lowering agents** (17, QD).
All patients received first prescriptions and were instructed to take the medication as prescribed. Followup was 6 months (gout 12 mo). All patients were aware of the monitoring capability of the package. At baseline a series of questionnaires was completed. We summarized the dosing histories as "taking compliance" (percentage of total prescribed doses taken), "correct dosing" (percentage of doses taken as prescribed), and "timing compliance" (percentage of doses taken within +/- 25% of prescribed interdose intervals). RESULTS: A total of 26,685 days (> 73 patient-years) were monitored. Compliance expressed as "taking compliance," mean (95% CI), "correct dosing," mean (95% CI), and "timing compliance," mean (95% CI) are: naproxen: 82% (75-90), 68% (57-80), 48% (34-61); diclofenac: 77% (61-93), 67% (47-87), 39% (21-57); MTX: 107% (98-117), 81% (75-87), 83% (76-90); SSZ: 72% (60-84), 55% (44-67), 25% (18-33); prednisolone: 96% (89-102), 88% (83-92), 82% (74-89); colchicine: 65% (48-81), 44% (26-62), 32% (18-46); and uric acid **lowering agents**: 84% (76-92), 74% (63-85), 65% (52-79).
Missed doses occurred more frequently than taking of extra doses: in RA, on 10% of all monitored days there was no evidence of dosing, while on 3% of all monitored days extra doses were taken. In PMR and gout these data are 10% and 4%, and 15% and 7%, respectively. We observed a decline of compliance over time in all study medication groups. Multiple regression analyses showed that the class of medication (symptom modifying or disease controlling), the dosing frequency, the patient's sex, coping pattern (avoidance, passive reaction pattern, and expression of emotions), and the overall health (total Nottingham Health Profile score) together explained 67% of the variance in taking compliance (adjusted R2) ($p = 0.002$).
CONCLUSION: Studying patient compliance with prescribed drug regimens utilizing electronic medication event monitors in RA, gout, and PMR showed that large differences exist in compliance between the various medication groups. Compliance declines over time. A regression model shows that it is possible to relate differences in patient compliance to a number of medication and patient related factors.

L9 ANSWER 8 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2001341624 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11342423
TITLE: A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis.
AUTHOR: Goldman S C; Holcenberg J S; Finklestein J Z; Hutchinson R; Kreissman S; Johnson F L; Tou C; Harvey E; Morris E; Cairo M S
CORPORATE SOURCE: Department of Pediatric Hematology/Oncology at North Texas Hospital for Children at Medical City, Dallas, TX, USA.
SOURCE: Blood, (2001 May 15) 97 (10) 2998-3003.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB Standard therapy in the United States for malignancy-associated hyperuricemia consists of hydration, alkalinization, and allopurinol. Urate oxidase catalyzes the enzymatic oxidation of uric acid to a 5 times increased urine soluble product, allantoin. Rasburicase is a new recombinant form of urate oxidase available for clinical evaluation. This multicenter randomized trial compared allopurinol to rasburicase in pediatric patients with leukemia or lymphoma at high risk for tumor lysis. Patients received the assigned **uric acid-lowering agent** for 5 to 7 days during induction chemotherapy. The primary efficacy end point was to compare the area under the serial plasma uric acid concentration curves during the first 96 hours of therapy (AUC(0-96)). Fifty-two patients were randomized at 6 sites. In an intent-to-treat analysis, the mean uric acid AUC(0-96) was 128 +/- 70 mg/dL.hour for the rasburicase group and 329 +/- 129 mg/dL.hour for the allopurinol group (P <.0001). The rasburicase versus allopurinol group experienced a 2.6-fold (95% CI: 2.0-3.4) less exposure to uric acid. Four hours after the first dose, patients randomized to rasburicase compared to allopurinol achieved an 86% versus 12% reduction (P <.0001) of initial plasma uric acid levels. No antirasburicase antibodies were detected at day 14. This randomized study demonstrated more rapid control and lower levels of plasma uric acid in patients at high risk for tumor lysis who received rasburicase compared to allopurinol. For pediatric patients with advanced stage lymphoma or high tumor burden leukemia, rasburicase is a safe and effective alternative to allopurinol during initial chemotherapy.

L9 ANSWER 9 OF 11 MEDLINE on STN
ACCESSION NUMBER: 1998260393 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9598031
TITLE: Decreased serum concentrations of 1,25(OH)2-vitamin D3 in patients with gout.
AUTHOR: Takahashi S; Yamamoto T; Moriwaki Y; Tsutsumi Z; Yamakita J; Higashino K
CORPORATE SOURCE: Third Department of Internal Medicine, Hyogo College of Medicine, Japan.
SOURCE: Advances in experimental medicine and biology, (1998) 431 57-60.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807

ENTRY DATE: Entered STN: 19980731
Last Updated on STN: 19980731
Entered Medline: 19980723

AB We measured the serum concentrations of 1,25(OH)2-vitamin D3, 25(OH)-vitamin D3, parathyroid hormone (PTH) in 82 male patients with primary gout whose serum uric acid was significantly higher than that of 41 normal control male subjects (8.8 +/- 0.2 vs 5.6 +/- 0.2 mg/dL, p < 0.001). The serum 1,25(OH)2-vitamin D3 concentration was significantly lower in the patients with gout compared with the control subjects (39.6 +/- 1.4 vs 44.8 +/- 1.7 pg/mL, p < 0.05), while no differences were observed between the two groups in either the serum concentration of 25(OH)-vitamin D3 or PTH. The administration of **uric acid lowering agent** to the patients for 1 year caused a significant increase in their serum 1,25(OH)2-vitamin D3 concentration which was associated with a significant decrease in their serum uric acid concentration. In contrast, the serum concentrations of 25(OH)-vitamin D3 and PTH were not affected by these drugs. These results suggest that uric acid per se may directly decrease the serum concentration of 1,25(OH)2-vitamin D3 in patients with gout by inhibiting 1-hydroxylase activity.

L9 ANSWER 10 OF 11 MEDLINE on STN
ACCESSION NUMBER: 94143504 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8310084
TITLE: Gout and pseudogout.
AUTHOR: Agarwal A K
CORPORATE SOURCE: Rheumatology Services, Medical Center, Beaver, Pennsylvania.
SOURCE: Primary care, (1993 Dec) 20 (4) 839-55. Ref: 27
Journal code: 0430463. ISSN: 0095-4543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19940330
Entered Medline: 19940315

AB This article describes the clinical spectrum of gout and pseudogout and discusses the role of colchicine, NSAIDs, and **uric acid --lowering agents** in the management of different stages of gout. A great majority of patients with gout are now seen and treated by primary care physicians. Strategy for successful management of gout and prevention of its disabling complications are discussed also.

L9 ANSWER 11 OF 11 MEDLINE on STN
ACCESSION NUMBER: 91136601 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1994910
TITLE: Persistence of monosodium urate crystals and low-grade inflammation in the synovial fluid of patients with untreated gout.
AUTHOR: Pascual E
CORPORATE SOURCE: Seccion de Reumatologia, Hospital de Alicante, Spain.
SOURCE: Arthritis and rheumatism, (1991 Feb) 34 (2) 141-5.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910405
Last Updated on STN: 19910405
Entered Medline: 19910319

AB Synovial fluid (SF) from 74 asymptomatic knees of patients with gout was analyzed. These patients had never been treated with serum **uric acid-lowering agents.** SF samples were analyzed for the presence of crystals and for cell counts, using undiluted SF directly in a Niebauer cell counting chamber. Thirty-seven of the aspirated knees had previously been inflamed, and monosodium urate (MSU) crystals were seen in SF aspirates from 36 of them (97%). Of the 37 knees that had never been inflamed, only 8 contained MSU crystals (P less than 0.00001). After reaching the joint, MSU crystals will persist in the SF as long as the serum uric acid level has not been lowered by appropriate treatment. In this situation, analysis of SF is an excellent diagnostic test for the intercritical gout. The mean cell count in the 44 SF samples that contained MSU crystals was 449/mm3 (95% confidence interval 310-589); the mean cell count in the 30 SF without MSU crystals was 64/mm3 (95% confidence interval 34-95) (P less than 0.00002). The SF samples that contained MSU crystals also had a higher percentage of polymorphonuclear leukocytes than those without MSU crystals (P less than 0.002). These data suggest that there is a low-grade inflammation present in the knees of patients with MSU crystals, the consequences of which should be investigated.

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=> d hist

     (FILE 'HOME' ENTERED AT 13:28:28 ON 01 APR 2005)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 13:28:43 ON 01 APR 2005
L1          1214 S XANTHINE OXIDASE INHIBITOR?
L2          1166 S XANTHINE OXIDASE INHIBITOR
L3        306913 S HYPERTENSION
L4            40 S L1 AND L3
L5          3548 S XANTHINE OXIDASE AND INHIBITION
L6            40 S L4 AND L4
L7         38472 S URIC ACID?
L8          2565 S L3 AND L7
L9            11 S URIC ACID LOWERING AGENT

=> s not hypertension
MISSING TERM BEFORE 'NOT'
Search expressions cannot begin with operators.

=> s blood pressure lowering
   1 FILES SEARCHED...
L10        5422 BLOOD PRESSURE LOWERING

=> s L1 and L10
L11           1 L1 AND L10

=> d l abs ibib
'L' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS ---------- GI and AB
ALL ---------- BIB, AB, IND, RE
APPS --------- AI, PRAI
BIB ---------- AN, plus Bibliographic Data and PI table (default)
CAN ---------- List of CA abstract numbers without answer numbers
CBIB --------- AN, plus Compressed Bibliographic Data
DALL --------- ALL, delimited (end of each field identified)
DMAX --------- MAX, delimited for post-processing
FAM ---------- AN, PI and PRAI in table, plus Patent Family data
FBIB --------- AN, BIB, plus Patent FAM
IND ---------- Indexing data
IPC ---------- International Patent Classifications
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MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field
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an arrow prompt (=>).  Examples of formats include: TI; TI,AU; BIB,ST;
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specification.

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FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

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     (FILE 'HOME' ENTERED AT 13:28:28 ON 01 APR 2005)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 13:28:43 ON 01 APR 2005
L1          1214 S XANTHINE OXIDASE INHIBITOR?
L2          1166 S XANTHINE OXIDASE INHIBITOR
L3        306913 S HYPERTENSION
L4            40 S L1 AND L3
L5          3548 S XANTHINE OXIDASE AND INHIBITION
L6            40 S L4 AND L4
L7         38472 S URIC ACID?
L8          2565 S L3 AND L7
L9            11 S URIC ACID LOWERING AGENT
L10         5422 S BLOOD PRESSURE LOWERING
L11            1 S L1 AND L10

=> d L11 IBIB  abs
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L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:10270 CAPLUS
DOCUMENT NUMBER: 136:64126
TITLE: Agent reducing uric acid levels for treatment of cardiovascular disease and hypertension
INVENTOR(S): Kivlighn, Salah, Johnson, Richard S.; Mazzali, Matilda
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; University of Washington
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002000210	A2	20020103	WO 2001-US20457		20010628
WO 2002000210	A3	20021024			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2413201	AA	20020103	CA 2001-2413201		20010628
US 2002019360	A1	20020214	US 2001-892505		20010628
EP 1317258	A2	20030611	EP 2001-946722		20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004517804	T2	20040617	JP 2002-504992		20010628
PRIORITY APPLN. INFO.:			US 2000-214825P	P	20000628
			WO 2001-US20457	W	20010628

AB This invention relates to a method for treating and preventing hypertension by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Addnl., the scope of the invention includes a method of treating coronary heart disease by administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. Allopurinol administered from the initiation of an oxonic acid diet prevented the development of hyperuricemia and hypertension. In hypertensive, hyperuricemic rats, either withdrawal of the oxonic acid or adding allopurinol also resulted in a reduction in the blood pressure in association with a fall in serum uric acid values.

=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	143.12	143.33
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-21.90	-21.90

STN INTERNATIONAL LOGOFF AT 14:00:24 ON 01 APR 2005